Strategies for cardiovascular prevention by Evidence Based Medicine

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Measure what is measurable, and make measurable what is not so.
Galileo Galilei

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Author's declaration

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Publications portfolio

1) Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, Chiariello M.

Does Intima-Media Thickness regression predict cardiovascular risk reduction? A meta-analysis of 41 randomized clinical trials

Journal of the American College of Cardiology; 2010; 56:2006-20.

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2) Costanzo P*, Savarese G*, Rosano G, Musella F, Casaretti L, Vassallo E, Paolillo S, Marsico F, Rengo G, Leosco D, Perrone-Filardi P

Left ventricular hypertrophy reduction and clinical events. A meta-regression analysis of 14 studies in 12,809 hypertensive patients.

International Journal of Cardiology;167:2757-64

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*Equal contribution

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3) Costanzo P, Perrone-Filardi P, Petretta M, Marciano C, Vassallo E, Gargiulo P, Paolillo S, Petretta A, Chiariello M.

Calcium channel blockers and cardiovascular outcomes: a meta-analysis of 175 634 patients.

Journal of Hypertension. 2009; 27:1136-51

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4) Savarese G*, Costanzo P*, Cleland JG, Vassallo E, Ruggiero D, Rosano G, Perrone-Filardi P.

A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure.

Journal of the American College of Cardiology. 2013;61:131-42

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5) Petretta M, Costanzo P, Perrone-Filardi P, Chiariello M.

Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis.

International Journal of Cardiology. 2010; 138:25-31

Impact Factor 5.5 Citations 78

Authors contribution: MP: hypothesis generation, manuscript review. PC: data collection, data analysis, manuscript drafting. PPF: manuscript review. MC manuscript review.

Full texts of the publications listed above are attached at the end of this thesis.

Impact factor and citations updated until July 2015

Abbreviations

ACE-I: Ace Inhibitor

ARB: Angiotensin Receptor Blocker

CCB: Calcium Channel Blocker

CHD: Coronary Ischaemic Disease

CI: Confidence Interval

IMT: Intima Media Thickness

LDL: Low Density Lipoprotein

LVH: Left Ventricular Hypertrophy

LVSD: Left Ventricular Systolic Dysfunction

MI: Myocardial Infarction

OR: Odds Ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta Analyses

QUOROM: Quality of Reporting Meta-analyses

RR: Relative Risk

Summary

Cardiovascular prevention aims to early identify patients at higher risk of developing a cardiovascular event, Prompt identification and treatment of those can potentially reduce the risk of events to occur

The purpose of this study was to assess the efficacy of drug therapy in primary and secondary cardiovascular prevention using the evidence based medicine approach.

In the first part of this thesis, the focus is on the role of two main surrogate end points for cardiovascular events, for which the prognostic role is still unclear (serial measurement of carotid intima-media thickness (IMT) and left ventricular hypertrophy (LVH))

In the second part, the efficacy of drug therapy strategies for cardiovascular events prevention is assessed for three topics lacking of clear evidence:
1) Calcium Channel Blockers (CCBs) and clinical outcomes
2) The role of Ace Inhibitors (ACE-Is) vs Angiotensin Receptor Blockers (ARBs) in patients without left ventricular systolic dysfunction
3) The efficacy of statin therapy in primary prevention according to the gender.

Literature review was performed by collecting all the articles relevant to the objectives of the study. A meta-regression analysis was performed to test the relationship between serial IMT or LVH changes and clinical outcomes. A meta-analysis was performed to calculate the overall estimates of effect of ACE-Is vs ARBs in patients without heart failure, of CCBs in hypertension or coronary artery disease and of statins in primary prevention according to gender. A publication bias test and sensitivity analysis were also performed.

The results showed that neither carotid IMT or LVH change predict the risk of cardiovascular events.

Furthermore, CCBs reduced the risk of myocardial infarction and were more effective than ACE-Is in preventing stroke, however they are possibly less effective than other medications in preventing heart failure.

In patients without heart failure, ARBs were not as effective as ACE-is in reducing cardiovascular outcomes.

Finally, statins in primary prevention of coronary heart disease appeared more effective in men than in women.

CHAPTER I

Introduction

Cardiovascular diseases mainly develop subclinically, often progressing to an advanced stage by the time the symptoms occur. It still remains the major cause of death worldwide. Prevention strategies have been crucial to reduce the incidence of cardiovascular events in either primary (when a cardiovascular event has not occurred) and secondary (when a cardiovascular event has already occurred) (1).

Cardiovascular research efforts have focused on trying to predict the probability of the occurrence of cardiovascular events and on the effectiveness of treatments to prevent them. This has led to the publications of several markers of disease progression called "surrogate end points" (2). The National Institutes of Health (USA) has defined surrogate endpoint as "biomarker intended to substitute for a clinical endpoint" (3). The concept is to assess the value of a treatment before the occurrence of a hard outcome (cardiovascular event or mortality mainly) (4).
Two of the most used cardiovascular surrogate end points are

1) The carotid intima-media thickness (IMT)
2) The left ventricular hypertrophy (LVH)

Carotid IMT and cardiovascular risk
Carotid IMT predicts the risk of cardiovascular events (5), with a relatively stronger prognostic power for cerebral as compared with coronary vascular events (6). In fact, increased IMT is considered to represent a manifestation of subclinical atherosclerosis, and, therefore, it has been included in the list of organ damage conditions in the European hypertension guidelines (7) and in the European prevention guidelines (8). The lack of invasiveness and repeatability makes IMT

measurement an attractive biomarker, potentially useful as a therapeutic target in subjects at increased cardiovascular risk (9). Therefore, IMT changes (either regression or slowed progression) have been used as a surrogate clinical end points in several randomized clinical studies using lipid-lowering agents (10-31), antihypertensive (32–38), oral anti-diabetic (39-41), and antioxidant drugs (42–45).

However, although clinical events were generally reported in these trials, none of them was designed to verify whether serial changes of IMT were associated with consistent changes of the cardiovascular risk profile (46). Yet, this information would be relevant for the interpretation of IMT variations as surrogate clinical end points and use as therapeutic targets for monitoring and optimization of cardiovascular therapies in several categories of subjects at increased cardiovascular risk (9,47).

LVH and cardiovascular risk

Considered as target organ damage, LVH represents an independent risk factor for death and major cardiovascular events including heart failure, coronary heart disease and stroke (7-8, 48-49).

Although the prognostic value of LVH has been long established, the prognostic value on cardiovascular outcomes of LVH regression, induced by medical treatments, has been a source of debate due to conflicting results of interventional studies (50-52). Cipriano and colleagues studied a small cohort of patients finding that LVH regression was not associated with reduction in cardiovascular events (50). Instead, Verdecchia and colleagues meta-analysis reported a substantial reduction of cardiovascular events events associated with reversal of LVH in hypertensive patients (51). Similarly, Pierdomenico and colleagues confirmed this observation in another larger meta-analysis, reporting a 54% reduction of cardiovascular events in patients with full regression of LVH (52). However, these studies assessed LVH qualitatively (presence vs absence of LVH at baseline and follow up), whilst the development of LVH is a continuous phenomenon and the association between the quantitative extent of LVH and cardiovascular risk has been also reported (53).

Therefore, it is conceivable that a similar continuous association between even a partial regression of LVH and reduction of event risk also may exist. Thus, even small regression of LVH may be associated with improved prognosis in hypertensive patients. However, the evidence is not clear, since no study has been performed with enough statistical power to assess the quantitative relationship between LVH regression and cardiovascular outcomes (54-66).

First Objective

Since the role of these two surrogate end points for cardiovascular events (IMT and LVH) is still debated, in the first part of this thesis I will assess the role of serial IMT measurements on the incidence of major cardiovascular events with a meta-regression analysis of all available randomized trials

In a similar fashion, I will assess the association between quantitative measurements of LVH and cardiovascular outcomes, with a meta-regression analysis of all available randomized trials will be

Cardiovascular prevention. Filling the gaps in the Evidence Based Medicine.

Among cardiovascular risk factors, a substantial portion of the global burden of cardiovascular disease and mortality is mainly carried by hypertension, hypercholesterolemia (67).
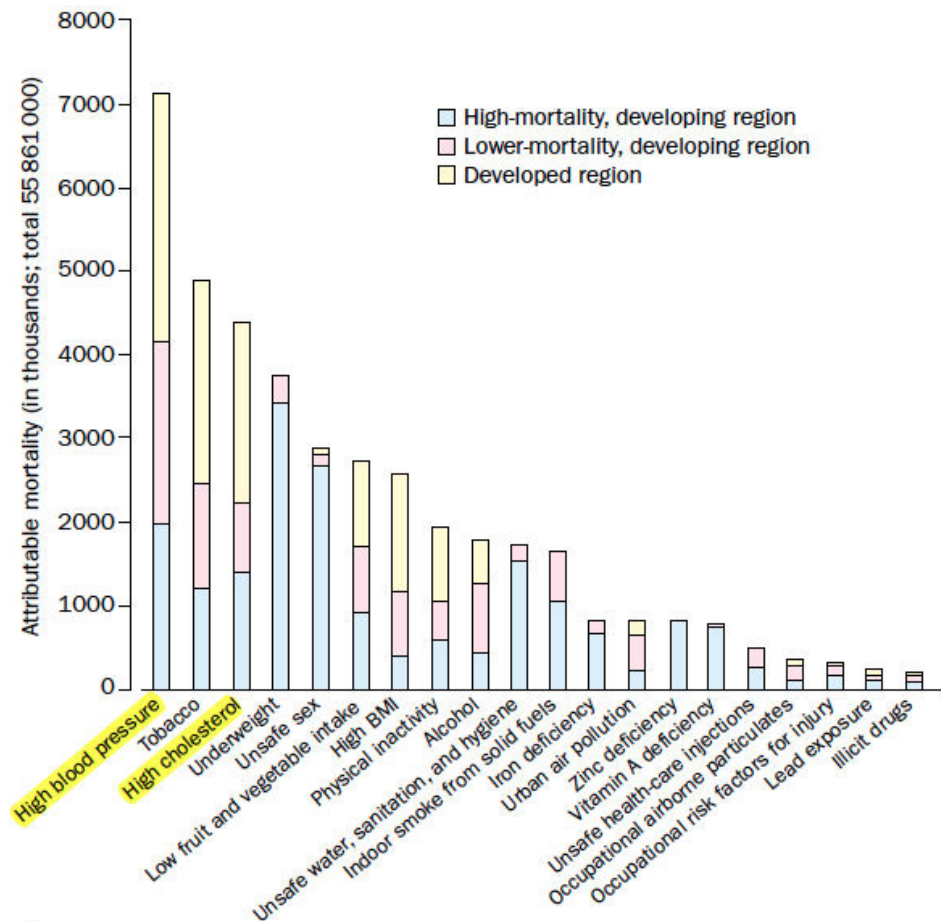
Figure 1. Attributable mortality according to risk factors in developed or developing country. From the Comparative Risk Assessment module of the global burden of disease (GBD) year 2000 (Adapted with permission from Ezzati et al).

In relative recent years, effective treatment of these risk factors has been the mainstream of cardiovascular prevention, with a reduction in mortality rates (68, 69). However, the burden of the disease and mortality, especially in developed countries remains high and yet there is more to be gained by further reducing the burden of these risk factors (70). Actions for lowering blood pressure and cholesterol

level include lowering salt intake, replacing saturated fats with polyunsaturated fats (71-72). Diets with high fruits and vegetables content and increased physical activity also improve cardiovascular risk factor profiles (73, 74). However, an increased uptake of such healthier habits in a population needs a systematic approach with a combination of policies and actions that are often found difficult to be implemented on a large scale. Therefore, so far, clinical management with anti-hypertensive and statin drug therapy has been the most effective way to tackle these risk factors (70).

Currently, the most recommended and used drugs for blood pressure lowering are ace-inhibitors (ACE-I), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), thiazidic diuretics and beta blockers (75).

In this research study the attention is particularly focused on three areas of pharmacological intervention where clear evidence is not available yet.

a) CCBs and clinical outcomes

b) The role of ARBs compared to ACE-Is in patients without heart failure

c) The efficacy of statin therapy in primary cardiovascular prevention according to the gender.

CCBs and clinical outcomes

Calcium channel blockers (CCBs) are broadly used antihypertensive and anti-angina agents. Their popularity is not only due to their blood pressure-lowering effects, but also to their effectiveness regardless of age or ethnic background (76).

Cardiovascular outcomes related to treatment with CCBs in hypertensive and also in coronary artery disease patients have been analysed in previous meta-analyses (77-80). In particular, in the late ninety, a meta-analysis published in the Lancet by Pahor and colleagues claimed an increased risk of cardiovascular outcomes with the use of CCBs. However, other studies have confuted those negative results (78-80), showing that CCBs are effective and safe. In fact, those previous concerns about CCBs were shown to be mainly driven by the inclusion in that meta-analysis of trials using short acting CCBs. In fact, in the same years became definitively clear that short acting CCBs were associated with an increased risk of myocardial infarction (81).

However, the prognostic evidence about CCBs was up to date only until 2003. Since then, the results of eleven large randomized clinical trials were published (82-91). The sum of the patients enrolled in these more recent trials nearly matches the sum of those enrolled in trials published until 2003. Therefore, although much investigation has been done on this topic, a meta-analysis including the results of these recent trials would provide more evidence on outcomes where there is still uncertainty for the use of CCBs. In fact, despite it has been clearly shown that long acting CCBs do not increase the risk of myocardial infarction and cardiovascular death, some doubts still remain about the risk of heart failure. In particular, previous meta-analyses showed an increased risk of heart failure associated with CCBs compared with other drugs (i.e. ACE-is) or a lack of protection towards developing heart failure compared with placebo (79, 80, 92).

The role of ACE-Is and ARBs in patients without left ventricular systolic dysfunction

It is well known that ACE-Is reduce mortality, hospital admissions for heart failure and myocardial infarction in patients with left ventricular systolic dysfunction (LVSD). These benefits are consistent also in patients without hypertension and are independent from blood pressure reduction (93). It has been then shown that ACE-Is reduce cardiovascular events also in patients without heart failure, at least in three major trials (94). The rationale for ACE-I therapy in patients without LVSD relies on the effects of vascular angiotensin II and bradykinin/prostaglandin system on the progression of atherosclerosis (95). However, during ACE-I therapy, Angiotensin II synthesis may shift to alternative ACE independent enzymatic pathways, which could reduce the efficacy of therapy (96). The unfavourable effects of angiotensin II on atherosclerosis progression are mediated through stimulation of angiotensin II receptor 1. ARBs prevent angiotensin II receptor 1 stimulation without direct effects on bradykinin/prostaglandin system, which improves their adverse effect profile compare to ACE-Is (96). Although ARBs reduce cardiovascular morbidity and mortality in patients with heart failure and reduce retinopathy and nephropathy in patients with diabetes mellitus (97-100), their effects in patients without heart failure are less certain, with major trials reporting conflicting results (101-110).

The efficacy of statin therapy in primary cardiovascular prevention according to male or female gender

It is known that the risk of cardiovascular events is lower in women than in men at any given age. This translates in a general perception of a relative cardiovascular protection of women at least until menopause. (111). This leads to a less aggressive approach to reduce cardiovascular risk factors and often to a less intense cholesterol management than men (112, 113). This could be one of the reasons why, despite an overall reduction in cardiovascular death in the last decades, the rate of this decline is smaller for women than for men (111).

Lipid-lowering treatment has been shown to reduce cardiovascular events in women with known coronary artery disease (secondary prevention). However, it is not clear yet whether this is true also in primary prevention (114). Despite a number of trials assessing lipid-lowering treatments have been performed, these only included a relatively small number of women, not enough to perform adequate gender-specific subgroup analysis. These primary prevention trials have been also assessed in a meta-analysis (115), however results were not stratified by gender. Two years later, in 2008, evidence that lipid-lowering treatment might reduces cardiovascular events in women were shown in a large Japanese statin trial treatment for primary prevention (116). This study included more than 5000 women, showing that pravastatin reduced cardiovascular events similarly in women and in men without previous cardiovascular disease.

Therefore, a clearer evidence for lipid lowering treatment in women for primary prevention would benefit from a meta-analysis that would include the results of this large study and those from previous smaller trials.

Second objective

The second objective of this study was to:

a) Update the previous meta-analyses with the results of the recent trials assessing the effect of CCBs treatment on all-cause mortality and cardiovascular events

b) The role of ARBs in patients without heart failure in preventing cardiovascular events, with an update of ACE-Is in the same setting.

c) The efficacy of statin therapy for primary cardiovascular prevention according to the gender.

CHAPTER II

METHODS

Trials search

The study was designed and conducted according to the QUOROM (Quality of Reporting Meta-analyses) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) (117,118). All the literature relevant to the objectives of this study was evaluated. The MEDLINE database, the Cochrane database, and the ISI Web of Science were searched for articles published in English and other languages. Principal investigators of the relevant studies were also contacted for data supplementation if required.

Two reviewers independently selected potentially eligible trials according to fulfilment of inclusion criteria. Selected trials were compared, and any discrepancies were resolved by discussion and consensus among authors.

Articles finally selected for the review were checked to avoid inclusion of data published in duplicate.

Carotid IMT trials search

Studies with the following criteria were included: evaluation of carotid IMT at baseline and at end of follow-up; report of major clinical cardiovascular end points (coronary heart disease events (CHD) including acute coronary syndrome, CHD death, revascularization; cerebrovascular (CBV) events, including transient ischemic attack and stroke, or all-cause death); comparison of active drug treatments or of an active drug versus placebo, or of different doses of active drugs. Only randomized studies were included, observational studies without longitudinal follow-up and cross-sectional studies were excluded.

Of 9,722 articles identified by the initial search, 85 were retrieved for more detailed evaluation, 41 were included in the study (Figure 2). In particular, 21 trials compared statins or other lipid-lowering drugs treatments versus placebo or active treatments, 8 trials compared

anti-hypertensive drugs versus active treatment or placebo 4 trials compared oral antidiabetic agents versus active treatment or placebo and 4 trials compared antioxidant agents versus placebo. Additionally, 1 trial compared an a:cholesterol acyltransferase inhibitor versus placebo, 1 trial compared estrogens versus placebo, 2 trials compared phosphodiesterase inhibitors versus placebo and 2 trials compared cholesteryl-ester transfer protein inhibitors versus placebo.
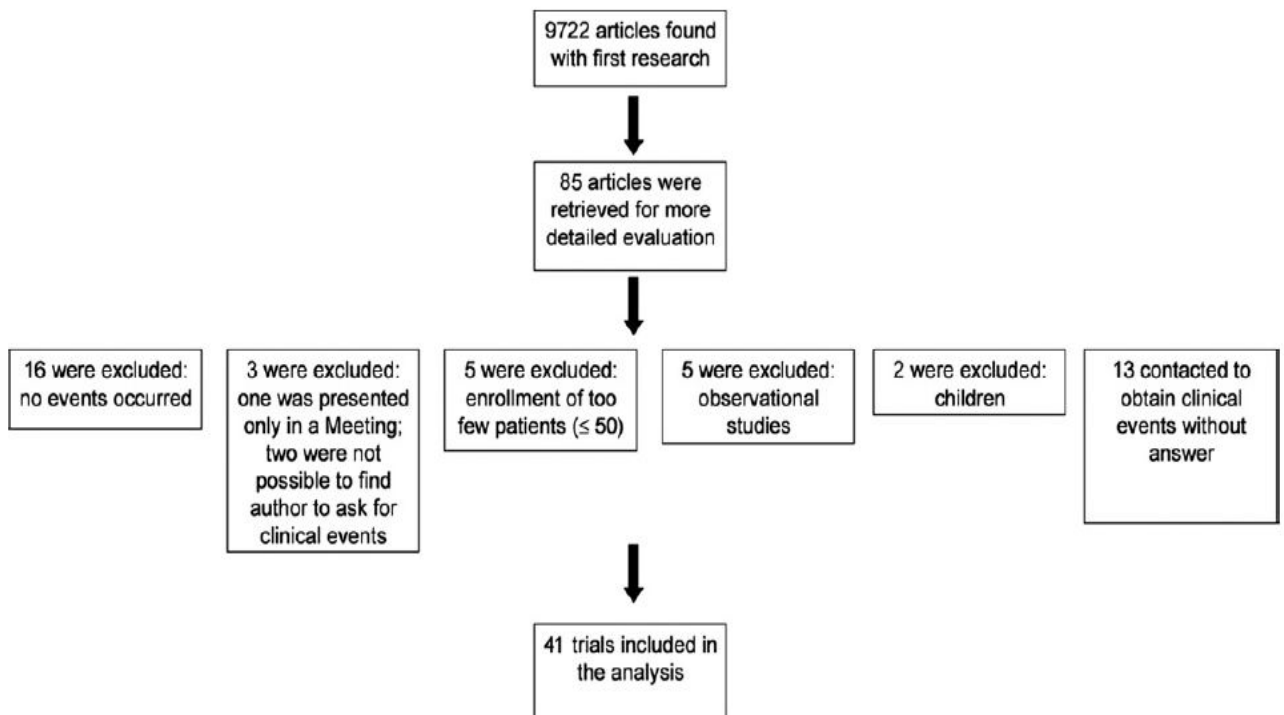
Figure 2. Flow chart of carotid IMT trials search

LVH trials search

Studies with the following criteria were included in the LVH meta-regression analysis: enrolment of hypertensive patients with evaluation of left ventricular mass by echocardiography or electrocardiography at baseline and at end of follow-up with quantification of changes of LVH parameters; reporting of at least one clinical event; comparison of active drug treatments or of an active

drug versus placebo, or of different doses of active drugs; randomized protocol design.

Of 2351 articles identified in the initial search, 30 were retrieved for more detailed evaluation and 14 were included in the study (Figure 3).
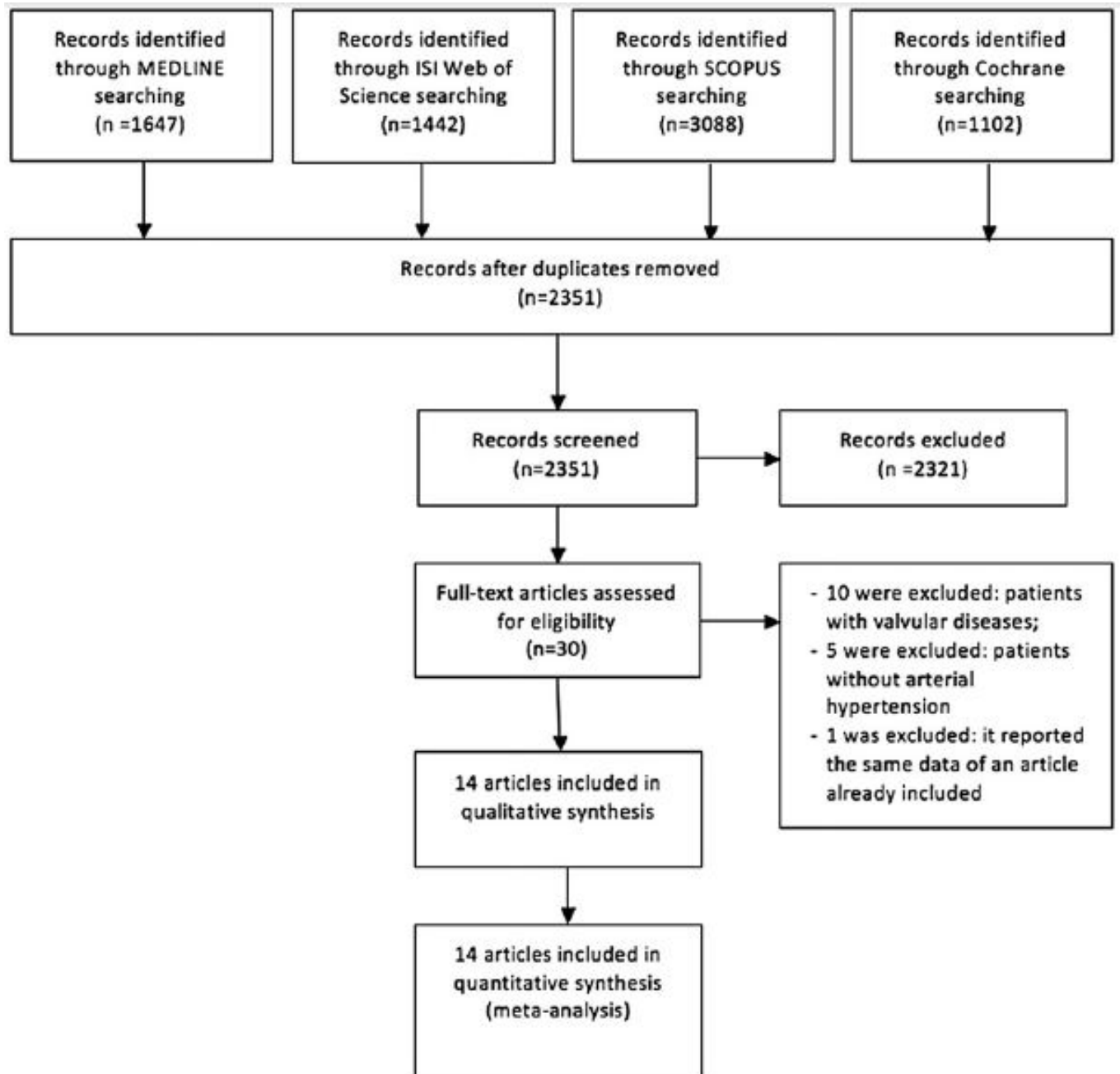
Figure 3. Flow chart of LVH trials search

CCBs trials search

Studies with the following criteria were included: comparison of a long-acting CCB with another antihypertensive drug, placebo or standard care and reporting of clinical outcomes.

The initial search identified 5661 articles, of those 29 were included according to all inclusion criteria (Figure 4).

Among these, two trials were then excluded (CASTEL and FACET, 119,120) for significant faults in their design (use of a short acting CCB in the former and retrospective collection of events in the latter, as also previously pointed out by the Blood Pressure Trialists Collaboration) (92).
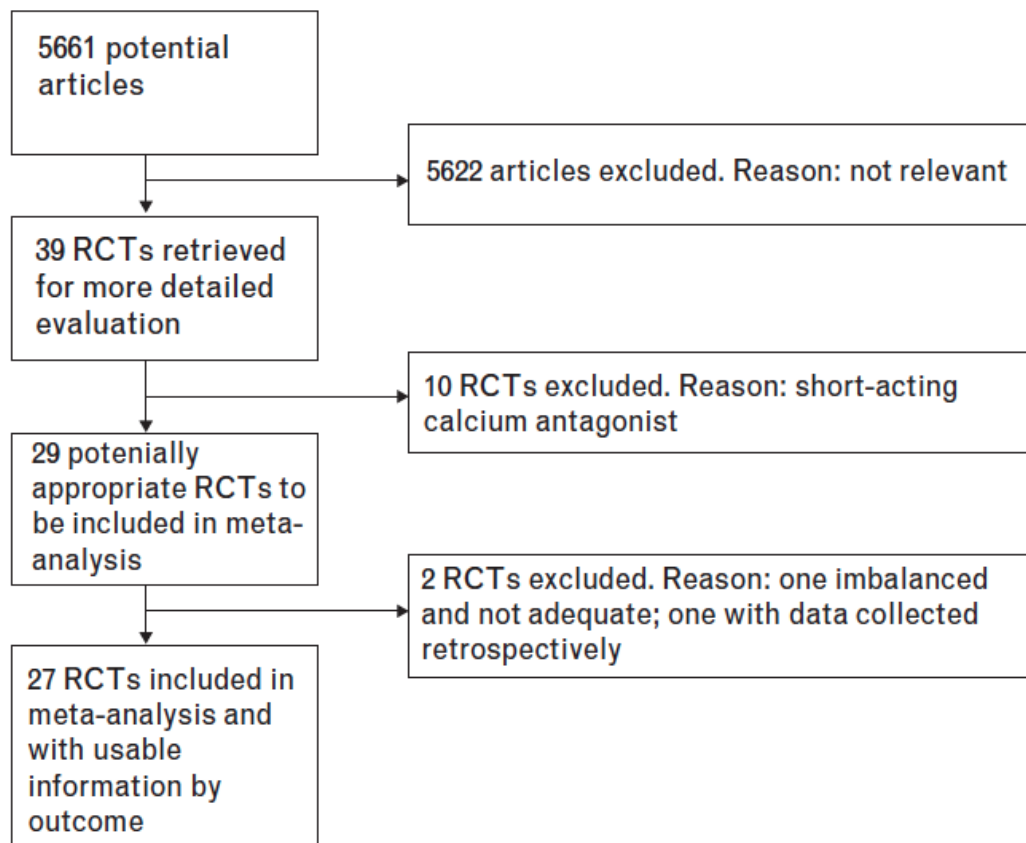
Figure 4 Flow chart of CCBs trials search.

ACE-Is vs ARBs trials search

Studies with the following criteria were included: randomized, double-blind, clinical trials comparing either an ARB or an ACE-I with placebo, excluding patients with systolic or diastolic heart failure and reporting clinical events (including all-cause and cardiovascular death, myocardial infarction (MI), stroke, new-onset heart failure, and new-onset diabetes mellitus).

Data on baseline characteristics, presence of diabetes mellitus, hypertension, coronary artery disease, and pre-specified outcomes, including all-cause and cardiovascular death, MI, stroke, new-onset heart failure, and new-onset diabetes mellitus, were obtained. The first objective of the study was to assess the effect of treatments on the composite outcome (cardiovascular death, MI, and stroke) and on all-cause death.

In addition, the effects of treatments on the risk of each component of the composite outcome, new-onset heart failure and new-onset diabetes mellitus were also explored.
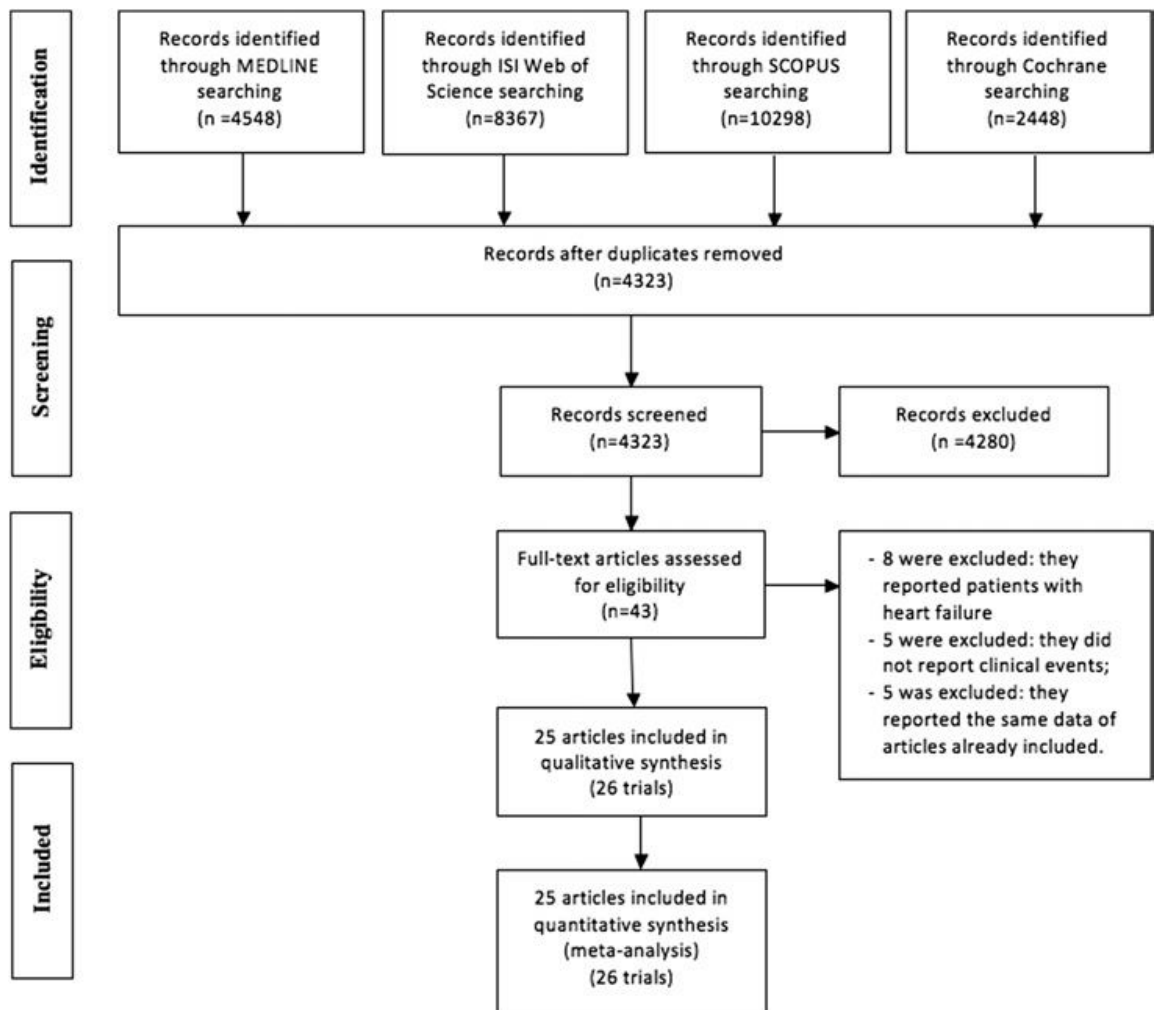
Figure 5. Flow chart of ACE-Is and ARBs trials search.

Statins trials search for primary cardiovascular prevention according to the gender

Studies with the following criteria were included:: randomized clinical trials of patients without known cardiovascular disease (primary prevention); available data on women and the effect of lipid-lowering drug therapy was assessed for clinical outcomes.

Data on the outcomes of total mortality, cardiovascular mortality, CHD events and revascularization procedures were extracted. The initial search identified 848 articles, of those 8 were included according to the above inclusion criteria (Figure 6).
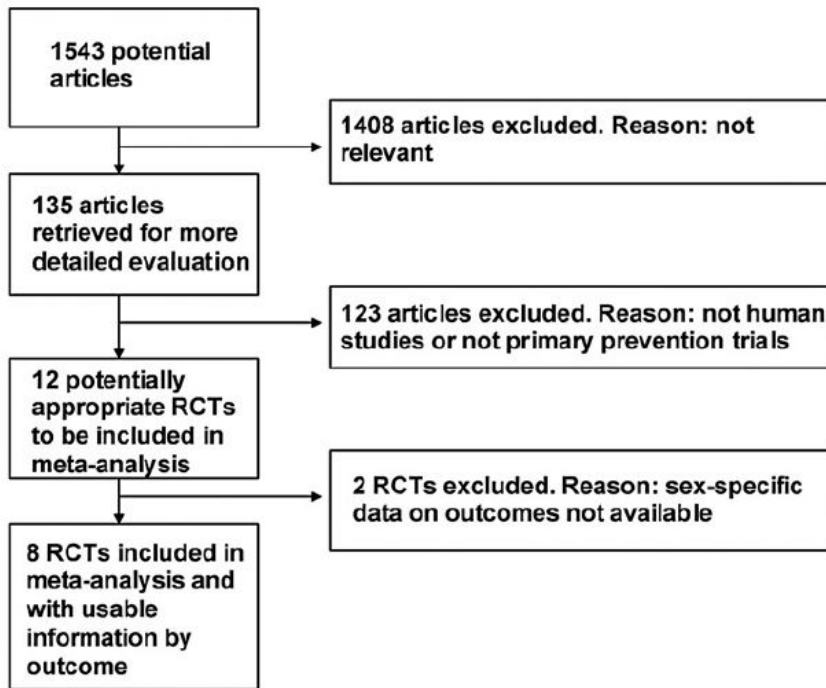
Figure 6. Flow chart of statins trial search in primary prevention in women or men.

Trials analysis

Meta-regression analysis of carotid IMT and LVH trials

Weighted random-effects meta-regression analysis was performed with the metareg command (121) (STATA version 11.0, StataCorps, College Station, Texas) to test the relationship between changes in IMT from baseline to end of follow-up and incidence of clinical events. Both mean and maximum IMT values were considered. Mean IMT was defined as the mean of all measurements on common carotid artery or, when this value was not available, a single measurement on common carotid artery. Maximum IMT was defined as the mean of all maximum measurements, or when this value was not available, the measurement at bulb or the single maximum value. The achieved differences between IMT change (millimetre per year) in the control group and the active treatment group both for mean and maximum IMT (delta mean IMT and delta maximum IMT, respectively) were considered. To explore the influence of potential effect modifiers on the association between IMT changes and outcomes, separate meta-regression analyses were performed also, including the following covariates, each separately: mean age, sex, body mass index, smokers, diabetes, hypertension, total serum cholesterol at baseline, low-density lipoprotein (LDL) at baseline and achieved difference between groups (from baseline to end of follow-up), systolic and diastolic blood pressure at baseline and achieved difference between groups (from baseline to end of follow-up), IMT mean and maximum at baseline, length of follow-up and study publication year. Meta-regression analysis was also performed to test the association between LDL cholesterol reduction and the outcomes. Quality of the trials were assessed with the Detsky score that measures randomization, blinding and statistical analysis, assigning a score from 0 – 21. The higher the score the better the quality of the study (122).

For all meta-regression analyses, a random-effects model was used to take into account the mean of a distribution of effects across studies. In fact, random-effects modelling more appropriately provides wider confidence intervals (CIs) for the regression coefficients than does a fixed-effect analysis, if residual heterogeneity exists (123).

To investigate a potential relationship between mean and maximum IMT modification and LDL serum level changes a linear regression analysis weighted by the size of each study was performed.

Meta-regression analysis of LVH trials.

Weighted random-effect meta-regression analysis was performed with the metareg command (121) (STATA Statacorp, version 11.0) to test the relationship between changes in LVH from baseline to end of follow-up and the occurrence of a composite outcome including all-cause death, MI, stroke and new onset heart failure. Additionally, the relationship between LVH changes and each component of the composite outcome was also analyzed. For this analysis, the percentage-achieved differences (delta) between change in control group and active treatment for LVH were considered. To explore the influence of potential effect modifiers on the association between LVH changes and outcomes, separate meta-regression analyses were performed including the following covariates, each one separately: mean age, sex, body mass index, systolic and

diastolic blood pressure at baseline and achieved difference between the trials arms (from baseline to end of follow-up), length of follow-up and study publication year, prevalence of diabetes mellitus and coronary artery disease.

For all meta-regression analyses, the random effects model was used to take in account the mean of a distribution of effects across studies for the reasons already explained for the carotid IMT meta-regression (123)

Sensitivity analysis for carotid IMT and LVH trials

Sensitivity analysis was performed to verify the robustness of the results. In detail, for carotid IMT trials, to assess the influence of the baseline profile risk, a separate meta-regression analysis was performed for primary and secondary prevention trials. To evaluate the specific effect of treatment category, meta-regression analysis was performed separately for treatment category (lipid lowering, anti-hypertensive, anti-diabetic, antioxidant therapy). To assess the influence of mean and maximum IMT baseline measures, these were used as covariates in meta-regression analysis.

Furthermore, the influence of several potential effect modifiers on the association between IMT changes and outcomes was also explored. Finally, as previously stated, IMT measurements were expressed in millimetres per year; however, we also performed the meta-regression analysis by using the achieved differences between IMT change in the control group and the active treatment group both for mean and maximum IMT.

To explore nonlinearity in the associations between each outcome and delta mean and maximum IMT, the splined models were also used (124, 125).

As per the LVH trials, meta-regression was separately performed for echocardiographic and electrocardiographic studies. Since studies included in meta-analysis differed in length of follow-up (0.5 to 5 years), a meta-regression analysis assessing the relationship between percentage changes in LVH per year and outcomes was performed. Additionally, to assess the influence of potential effect modifiers, analyses were performed also including different covariates (i.e age, gender, blood pressure etc. see results).

Meta-analysis of CCB, ACE-Is-ARBs and primary prevention statin trials

Effects of randomized treatments were analyzed with the metan routine (126) (STATA version 11.0, StataCorps, College Station, Texas). Odds ratios (ORs) and 95% CI for every outcome were calculated separately for each trial for the CCBs and ACE-Is-ARBs meta-analyses. The choice to use the OR was driven by the need of performing meta-regression for sensitivity analysis for both CCBs and ACE-Is-ARBs. In fact, theoretical mathematical arguments support OR rather than Relative Risk (RR) in the setting of regression analysis (127). In fact, OR were also used with the carotid IMT and LVH trials in order to evaluate the meta-regression against the outcome analysis.

However, for meta-analysis assessing the role of statins in primary prevention of cardiovascular events in women the RR has been used. This choice was due to the fact that meta-regression analysis was not planned. Furthermore, the baseline risk of the population was low (primary prevention), therefore the RR would have avoided the risk of overestimation of the outcome (128).

In detail, ORs were calculated with fixed-effects, random effects model or Peto method where appropriate. The assumption of homogeneity between the treatment effects in different trials was tested with the Q and the I square statistic. If the assumption of homogeneity was rejected (P< 0.10), additional analyses were done with a random effects model and sensitivity analysis (129). Furthermore, if events rate were 1% or less analysis was also performed with Peto method (130). Pooled ORs were logarithmically transformed and weighted for the inverse of variance. Since for every outcome there was always at least a trial with an event rate of 1% or less, the ORs showed in the results are referred to Peto method.

For the statins trials RR and 95% CIs for each outcome were calculated separately for each trial. Overall estimates of effect were

calculated with inverse-variance model (131). We used this method, and not fixed effect model, because one study (83) reported only RR, and not the number of events, thus it was not possible to enter continuous data (number of events) for this trial (132).

Participants could contribute only with one event to the calculation for each outcome but could contribute with one event to each of the separate analyses of different outcomes.

The significance level for the overall estimates of effect was set at p value of less than 0.05.

Sensitivity Analysis for CCBs, ACE-ARBs and statins for primary prevention according to the gender

A sensitivity analysis to assess the robustness of the results was performed.

In detail, for CCBs trials, the influence of placebo trials was assessed, by including and excluding them. Separate analysis for dihydropyridine and non-dihydropyridine CCBs was performed. Trials with outstanding results that could have biased this meta-analysis were also included and excluded to evaluate their effect on the overall meta-analysis. Finally, a separate analysis for CCBs versus different classes of drugs was performed.

For both CCBs and ACE-Is and ARBs meta-analysis, a meta-regression analysis (with the same methodology as explained above for IMT and LVH) was performed to test the relationship between outcomes and potential effect modifiers (i.e. age, gender, blood pressure etc. see results) and to investigate potential sources of heterogeneity among different trials, in case of statistical evidence of it.

For statins in primary prevention of cardiovascular events according to the gender, we assessed the effect of those studies that appeared

to be outliers, by evaluating their influence on the RR by including and excluding them. Particular attention was focused on studies with a large population (83) or with results significantly outlying from the rest of the studies, (83) or if they were not entirely of primary prevention (133, 134) (i.e. including patients with previous cardiovascular disease).

Publication bias

To evaluate potential publication bias a rank correlation method proposed by Begg and Mazumdarand (135), a linear regression approach (136) and a modified Macaskill's test were used (137). The last one has become more popular in recent years having been shown to give more balanced type I error rates in the tail probability areas compared with other publication bias tests

CHAPTER III

RESULTS

Surrogate end points and cardiovascular events

Carotid IMT meta-regression analysis

Despite the active cardiovascular treatment reduced the risk of clinical events compared to placebo, neither carotid IMT or LVH progression or regression predicted the risk of them.

In detail, for carotid IMT trials, the baseline characteristics of the 41 trials (18,307 participants) included in the meta-analysis are shown in Table 1. 9,313 subjects were assigned to a statin and 8,994 to another drug or to placebo. The duration of follow-up ranged from 0.5 to 5 years, and the mean was 2.4±1 years. The overall mean age of subjects was 58±5 years and 43% were women.

Despite a significant reduction induced by active treatments in ischemic heart disease (OR 0.82; 95% CI 0.69-0.96; p=0.02), cerebrovascular events (OR 0.71; 95% CI 0.51-1; p=0.05) and all-cause death (OR 0.71; 95% CI 0.53-0.96; p=0.03), carotid IMT change did not significantly predict any of the above outcomes (Tau^2 range 0.32 - 0.91; p for each outcome >0.05) (Figure 8). In addition, baseline characteristics, cardiovascular risk profile, IMT at baseline, follow-up length, and quality of the trials did not significantly influence the association between IMT changes and clinical outcomes.

Sensitivity analysis was performed to assess the association between IMT changes and outcomes seperetely for primary and secondary prevention trials, for lipid lowering, antihypertensive, anti-diabetic and antioxidant therapy. Similar to the overall pooled analysis, no significant relationship between IMT changes and outcomes was observed in any of these separate analyses. Analyzing the influence of covariates listed above, the only notable result was that in primary prevention, reduction in systolic blood pressure significantly influenced the association between

Trial	Year	Treatment Category	Treatment	Control	Age years	Treatment N	Control N	Women %	BMI kg/m2	Follow-Up years	Smokers %	HTN %	Diabetes %	IHD %
ACAPS	1994	Lipid lowering	Lovastatin	Placebo	62	460	459	48	26	3	12	29	2	0
Angerer et al.	2001	Antioxidants	Fish oil/PUFA	Placebo	58	87	84	18	NR	2	15	48	0	53
ARBITER	2002	Lipid lowering	Atorvastatin	Pravastatin	60	79	82	29	NR	1	10	69	10	46
ARBITER 2	2004	Lipid lowering	Niacin+statin	Statin	67	87	80	9	NR	1	10	75	27	43
ASAP	2001	Lipid lowering	Atorvastatin	Simvastatin	48	160	165	61	26	2	32	NR	NR	31
ASFAST	2006	Antioxidants	Folic acid/vitamin B12	Placebo	56	156	159	51	26	3.6	10	90	23	21
ATIC	2007	Lipid lowering	Pravastatin	Placebo	53	47	46	43	27	2	35	31	0	0
BCAPS statin only	2001	Lipid lowering	Fluvastatin	Placebo	62	395	398	54	26	3	31	12	3	4
BCAPS statin+beta-blocker	2001	Anti-HTN	Metoprolol	Placebo	62	396	397	54	26	3	31	12	3	4
Beishuizien et al.	2004	Lipid lowering	Cerivastatin	Placebo	59	125	125	40	31	2	24	50	100	0
BVAIT	2009	Antioxidants	Folic acid/vitamin B12	Placebo	61	254	252	39	30	3	3	NR	NR	NR
CAIUS	1996	Lipid lowering	Pravastatin	Placebo	55	151	154	47	25	3	24	NR	NR	0
CAPTIVATE	2009	Lipid lowering	Pactimibe+statin	Statin	55	443	438	39	28	1.25	16	29	5	65
DAPHNE	2002	Anti-HTN	Doxazosin	HCT	59	41	39	0	26	3	46	100	0	39
ELSA	2002	Anti-HTN	Lacidipine	Atenolol	56	755	764	45	27	3.75	20	100	NR	NR
ENHANCE	2008	Lipid lowering	Simvastatin+ezetimibe	Simvastatin	46	357	363	51	27	2	28	16	2	28

Trial	Year	Treatment Category	Treatment	Control	Age years	Treatment N	Control N	Women %	BMI kg/m2	Follow-Up years	Smokers %	HTN %	Diabetes %	CHD %
EPAT	2001	Other	Estradiol	Placebo	61	97	102	100	29	2	0	0	3	0
FAST	2002	Lipid lowering	Pravastatin	Placebo	66	83	163	73	23	2	53	41	23	14
FIELD	2008	Lipid lowering	Fenofibrate	Placebo	62	87	83	37	29	5	14	56	100	20
Hodis et al.	2006	Oral antidiabetics	Troglitazone	Placebo	53	142	134	67	32	2	NR	67	100	0
HYRIM	2004	Lipid lowering	Fluvastatin	Placebo	57	142	143	NR	29	4	15	100	NR	0
KAPS	1995	Lipid lowering	Pravastatin	Placebo	57	224	223	0	NR	3	26	33	2	8
Mazzon	2006	Oral antidiabetics	Pioglitazone	Glimepiride	59	230	228	63	32	1.3	NR	70	100	18
METEOR	2007	Lipid lowering	Rosuvastatin	Placebo	57	702	282	40	27	2	22	28	0	0
MIDAS	1996	Anti-HTN	Isradipine	HCT	58	442	441	22	28	3	20	100	0	4
MITEC	2009	Anti-HTN	Candesartan	Amlodipine	60	100	109	63	31	3	NR	100	100	NR
Mitsuhashi	2004	Other	Cilostazol	Placebo	63	31	31	35	24	1	NR	60	100	0
PHYLLIS	2004	Lipid lowering	Pravastatin	Placebo	58	254	254	60	NR	3	16	100	NR	0
PLAC II	1995	Lipid lowering	Pravastatin	Placebo		75	76	NR	NR	3	NR	NR	NR	100
PREVEND IT	2005	Lipid lowering	Pravastatin	Placebo	51	317	325	37	NR	2	39	224	4	3
RADIANCE 1	2007	Lipid lowering	Torcetrapib+atorvastatin	Atorvastatin	46	450	454	49	27	2	20	24	3	0

Trial	Year	Treatment Category	Treatment	Control	Age years	Treatment N	Control N	Women %	BMI kg/m2	Follow-Up years	Smokers %	HTN %	Diabetes %	CHD %
RADIANCE 2	2007	Lipid lowering	Torcetrapib+atorvastatin	Atorvastatin	57	377	375	64	30	2	16	50	21	0
RAS	2007	Oral antidiabetics	Rosiglitazone	Placebo	68	277	278	51	30	1	13	57	36	7
REGRESS	1998	Lipid lowering	Pravastatin	Placebo	56	131	124	0	26	2	32	26	NR	100
RIS	1996	Lipid lowering	Life-style	Usual care	66	81	83	0	27	3.4	35	100	NR	
SANDS	2008	Lipid lowering	Standard statin treatment	Statin + ezetimibe)	56	223	204	67	34	3	19	NR	100	0
Shinoda-Tagawa	2002	Other	Cilostazol	Placebo	60	43	46	49	23	3.2	NR	57	100	NR
Stanton et al.	2001	Anti-HTN	Amlodipine	Lisinopril	49	35	34	40	NR	1	27	100	0	0
STARR ACE inhibitor	2009	Anti-HTN	Ramipril	Placebo	54	715	710	55	30	3	11	41	0	0
STARR glitazone	2009	Oral antidiabetics	Rosiglitazone	Placebo	54	709	716	55	30	3	11	40	0	0
VEAPS	2002	Antioxidants	Vitamin E	Placebo	56	162	170	NR	NR	3	36	0	0	0
VHAS	1998	Anti-HTN	Verapamil	Chlorthalidone	54	244	254	48	27	4	18	100	NR	NR
Yu	2007	Lipid lowering	Atorvastatin	Atorvastatin	66	57	55	17	NR	1	43	51	28	100

Table 1. Trials assessing drug therapy on serial IMT measurements (adapted from Publication 1). Abbreviations: BMI (Body Mass Index). NR (Not Reported). HTN (Hypertension). IHD (Ischaemic Heart Disease)
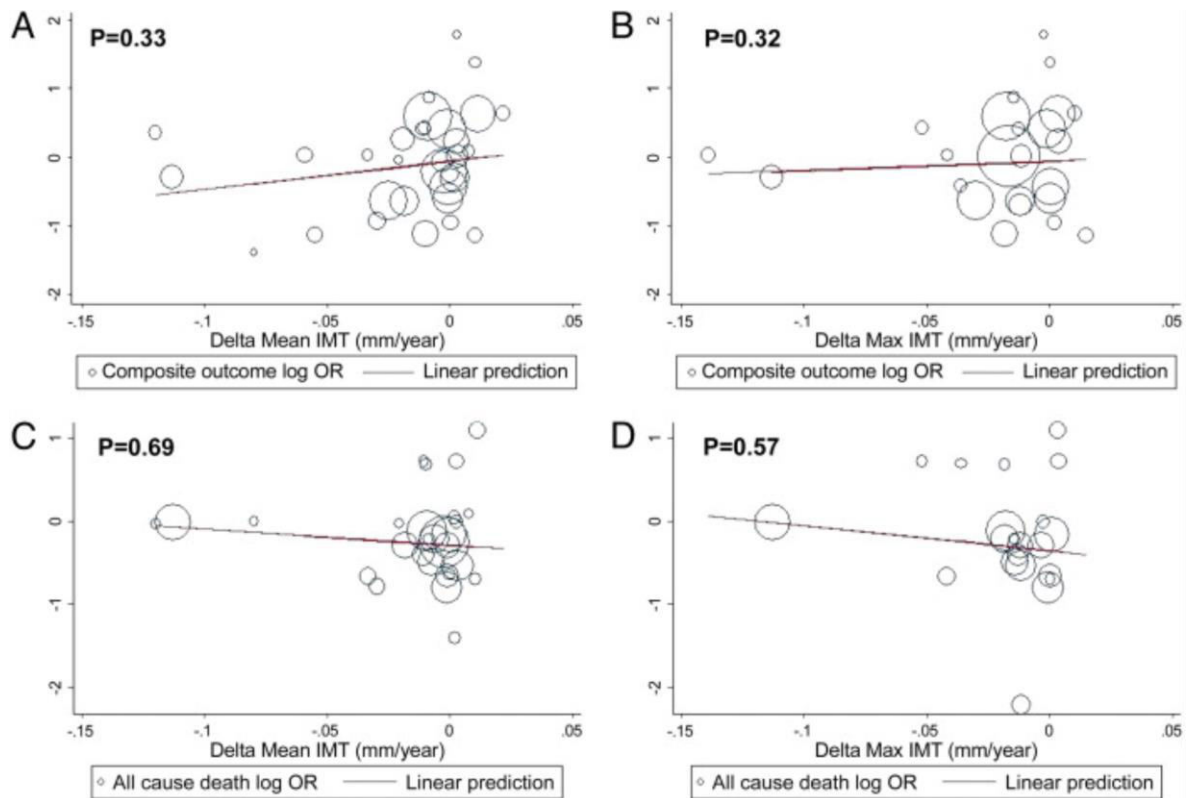
Figure 8. Meta-Regression Analysis Between Delta Mean and Maximum IMT, Composite Outcome, and All-Cause Death Meta-regression analysis between delta mean and maximum (max) intima-media thickness (IMT) for **(A, B)** composite outcome and **(C, D)** all-cause death. Log of odds ratios (OR) is reported on the y-axis, and the covariate is reported on the x-axis. Bubble size for each study is proportional to the inverse of the variance

maximum IMT changes and CHD risk reduction (change in tau 3.19 p=0.015).

We also performed a meta-regression analysis considering separately progression and regression of carotid mean and maximum IMT, and also in this case, no significant association between change in IMT and outcomes was observed. The influence of mean and maximum baseline IMT value was considered, including them as covariates in the analysis, and performing a meta-regression analysis in trials with mean or maximum IMT ≥ 1mm. Again, in both cases no significant association was found.

The analysis was also performed by using the IMT percent change from baseline, however the results did not significantly differ. Exploring a potential nonlinearity in the associations between the outcomes and delta mean and maximum IMT with the splined model (131) did not show any significant nonlinear relationship for all outcomes.

In addition, lack of relationship was confirmed when pre-specified potential effect modifiers were considered in the meta-regression analysis (age, sex, body mass index, smokers, diabetes, hypertension, total serum cholesterol at baseline, low-density lipoprotein (LDL) at baseline and achieved difference between groups (from baseline to end of follow-up), systolic and diastolic blood pressure at baseline and achieved difference between groups (from baseline to end of follow-up), IMT mean and maximum at baseline, length of follow-up, Detsky quality score (122), and study publication year.

In contrast, meta-regression analysis of lipid-lowering trials demonstrated a significant relationship between LDL lowering and reduction of CHD events and composite outcome with a trend for CBV events and no statistically significant association for all-cause death (Figure 9).

Furthermore, change in mean or maximum IMT was not associated with LDL serum changes.

Finally, no publication bias for any of the outcomes with Begg, Egger or Macaskill's modified test was found.
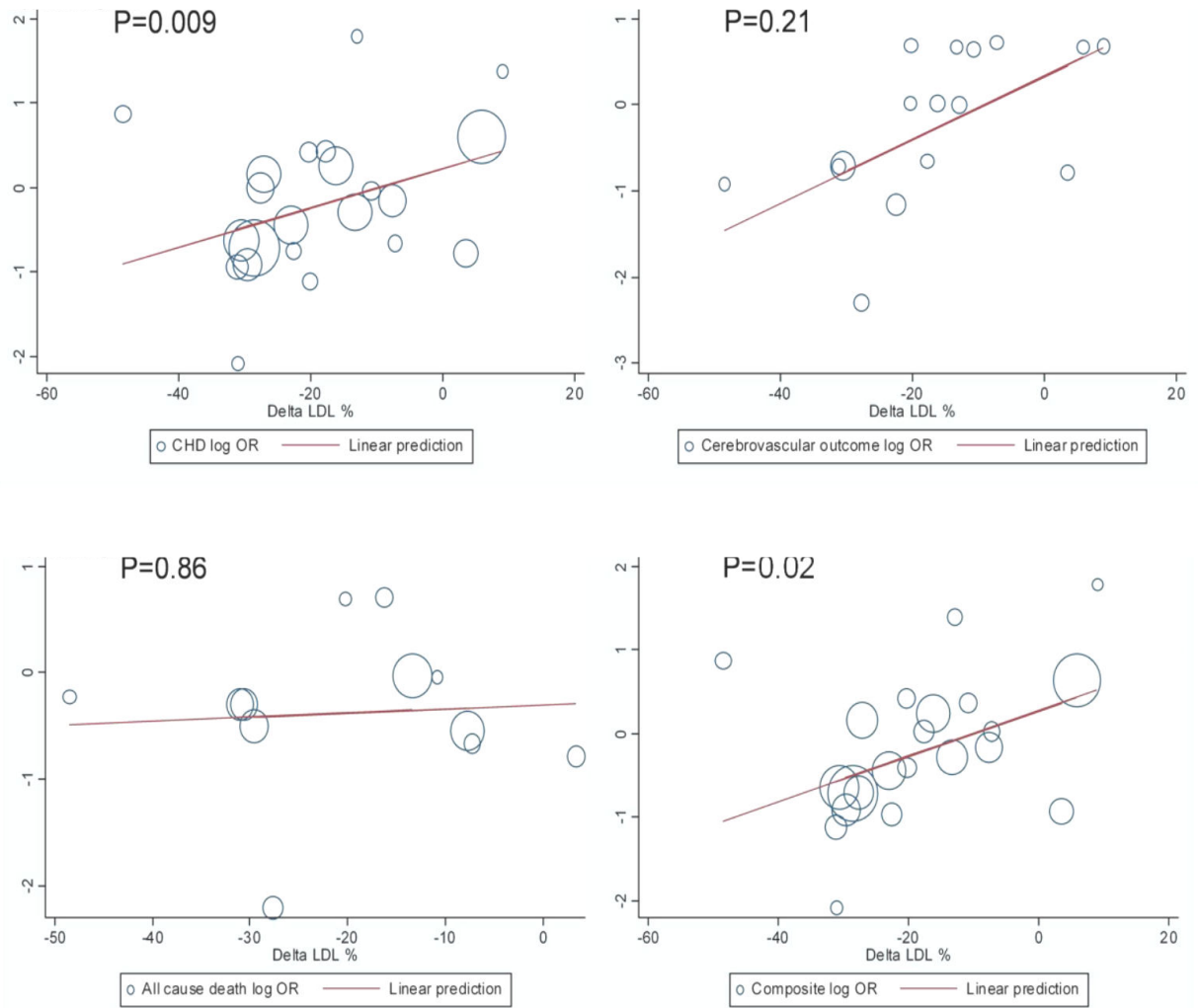
Figure 9. Meta-regression analysis of delta low-density lipoprotein (LDL) induced change (%), coronary heart disease (CHD), and cerebrovascular events (top); composite outcome and all cause death (bottom). Log of odds ratios are reported in the y-axis and covariate in the x-axis. CHD:Tau 2.9; p = 0.009; 95% CI 1.01-1.05. Cerebrovascular events: Tau 1.3; p = 0.21; 95% CI 0.98-1.1. Composite outcome: Tau 2.56; p = 0.02; 95% CI 1-1.05. All-cause death: Tau 0.18; p = 0.86; 95% CI 0.95-1.05. Bubble size for each study is proportional to the inverse of the variance.

LVH meta-regression analysis

The baseline characteristics of the 12,809 patients reported in the 14 trials
(54-66) (12,809 participants) included in meta-analysis are reported in Table 2. In detail, 6,444 subjects were assigned to treatment groups and 6,365 to control groups. The duration of follow-up ranged from 0.50 to 5 years, with mean 1.97±1.50 years. Mean age was 62±5 years and 52% of patients were women. A total of 2,259 events were reported among 12,809 patients included in the meta-analysis. LVH was assessed with echocardiography in 12 studies and by electrocardiography in 3 studies.

Pooling all trials included in the meta-analysis, the risk of composite outcome was significantly reduced by treatments vs control (OR 0.85; 95% CI 0.78-0.93; p<0.001). Similarly, the risk of stroke was significantly lower in the treatment group than control (OR 0.76; 95% CI 0.64-0.89; p<0.001). However, the risk of all-cause death (OR: 0.88, 95% CI 0.76-1.01; p=0.072), CHD (OR 1.031, 95% CI 0.85-1.25; p=0.763) or new onset heart failure (OR: 0.994; 95% CI 0.90-1.24; p=0.95) were not significantly reduced by treatment arms.

Meta-regression analysis showed that LVH reduction did not predict the composite outcome (Tau 0.69, p=0.5; Figure 10) nor any single components of the composite outcome, namely all-cause death (Tau -1.27, p=0.26), stroke (Tau 0.15, p=0.89), myocardial infarction (Tau 1.20, p=0.28) and new onset heart failure (Tau 1.7, p=0.33)

Trial	Year	Treatment category	Treatment	Control	Treatment (N)	Control (N)	Age (years)	Women (%)	BMI (kg/m2)	SBP (mmHg)	DBP (mmHg)	Diabetes (%)	Follow-up (years)
ABCD	2003	ACE-I	Enalapril	Nisoldipine	235	233	58	14	32	156	98	100	5
DEFEND	2010	Anti-HTN	Community care	Conventional therapy	33	32	62	46	36	161	87	100	1
ELVERA	2001	ACE-I	Lisinopril	Amlodipine	85	81	67	45	28	172	93	NR	2
Gerritsen et al	1998	CCB	Nitrendipine	Placebo	40	41	64	58	28	167	92	100	0.9
Heesen et al	2001	ACE-I	Lisinopril	Placebo	48	49	68	48	28	135	76	5	1
HYCAR	1995	ACE-I	Ramipril	Placebo	75	40	54	62	NR	138	86	NR	0.5
J-ELAN	2010	ARB	Losartan	Amlodipine	29	28	61	21	NA	153	93	25	1.5
JMS-1	2008	Alpha Blocker	Doxazosine	Conventional therapy	308	303	70	56	24	NR	NR	16	0.5
LIFE	2002	ARB	Losartan	Atenolol	4605	4588	67	54	28	174	98	13	4
REGAAL	2002	ARB	Losartan	Atenolol	115	110	57	32	NA	167	98	NA	0.7
RENAAL	2005	ARB	Losartan	Placebo	88	99	NR	NR	NR	159	83	NR	3.4
SANDS	2008	Anti-HTN	Intensive therapy	Conventional therapy	252	247	56	66	34	130	75	100	3
VALIDD	2007	ARB	Valsartan	Placebo	186	198	60	51	31	144	86	13	0.7
VART	2011	ARB	Valsartan	Amlodipine	305	316	61	45	40	156	93	9	3.4
		ACE-I	Enalapril	Placebo	40	41	61	67	28	166	93	100	0.9

Table 2. Trials assessing LVH progression (adapted from **Publication 2**). Abbreviations: ACE-I: Ace-Inihibitor. ARB: Angiotensin Receptor Blocker. CCB: Calcium Channel Blocker. BMI (Body Mass Index). DBP: Diastolic Blood Pressure. HTN: Hypertension. N: Number. NR (Not Reported). SBP (Systolic Blood Pressure).
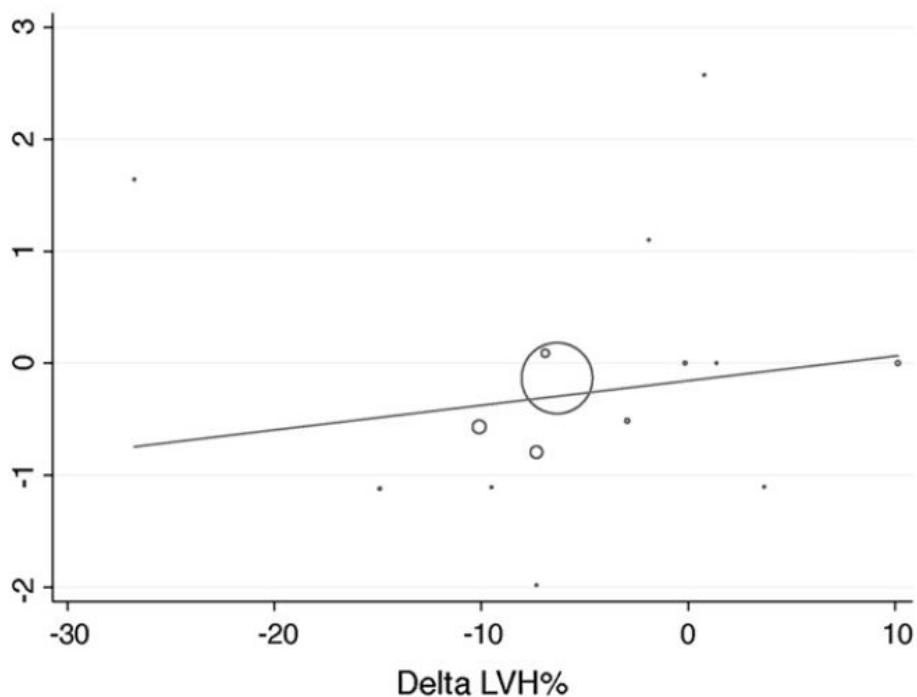
Figure 10. Meta-regression between ΔLVH and composite outcome. Tau 0.69 p=0.5.). Log of odds ratios are reported in the y-axis.

As per sensitivity analysis, no relationship between changes in LVH and outcomes was identified when meta-regression analyses were separately performed in each treatment group, or restricted to only echocardiographic or only electrocardiographic studies. Similarly, no relationship between changes in LVH and outcomes was shown using percent changes in LVH as covariate.

The relationship between LVH changes and outcomes was independent from systolic and diastolic blood pressure reduction, as shown by covariate meta-regression analysis. Furthermore, no additional covariate (age, body mass index, percent of women, year of publication, follow up length, systolic and diastolic blood pressure at baseline, prevalence of DM and CAD) significantly influenced the results.

Cardiovascular prevention. Where the evidence based medicine is not that "evident" yet

CCBs and clinical outcomes

The effect of CCBs in hypertension was evaluated in 27 trials. The baseline characteristics of the 27 trials with 175,634 patients included in the meta-analysis are shown in Table 3; 78,240 were assigned to a CCB and 97,394 to another drug or to placebo. The duration of follow-up ranged from 0.3 to 5.5 years with a mean of 3.4±1.2 years. The overall mean age was 64±5.8 years, 37% were women (Table 3).

The risk of all-cause death was reduced by CCBs compared with non-CCB-based regimen (OR 0.96; 95% CI 0.93–0.99; p<0.05). However, that was true only with dihydropyridine CCBs (OR 0.95; 95% CI 0.92–0.99; p<0.01) and not with non-dihydropyridine CCBs (OR 1.01; 95% CI 0.94–1.09; p=0.81) (Figure 11). Furthermore, this reduction in all-cause death remained when placebo trials were excluded (OR 0.96; 95% CI 0.92–0.99; p<0.05).

The risk of cardiovascular death was not reduced by CCBs compared with non-CCB therapy (OR 0.97; 95% CI 0.93–1.02; p=0.24) (Figure 12). CCBs were not inferior to ACE-is (OR 0.97; 95% CI 0.88–1.07; p=0.57).

CCBs compared with placebo decreased the risk of major cardiovascular events (OR 0.76; 95% CI 0.62–0.93; p<0.01). Furthermore, considering placebo and non-placebo trials, CCBs were not inferior to ACE-is for this outcome (OR 1.16; 95% CI 0.96–1.4; p=0.12) (Figure 13).

CCBs decreased the risk of heart failure compared with placebo (OR

0.72; 95% CI 0.59–0.87; p<0.001). However, ACE-is, B-Blockers and or diuretics were superior in reducing the risk of heart failure compared with CCBs when compared all together (OR 1.19; 95% CI 1.08–1.31; p<0.001) or individually (Figure 14).

Trial	Year	Treatment	Control	Indication	Study design	Patients (N)	Difference SBP	Difference DBP	Age	Diabetes %	Women %	Smokers %	Follow-up
AASK	2001	Amlodipine	Ramipril	HTN	Open	653	0.6	0.5	54	NR	39	NR	3
ABCD	1998	Nisoldipine	Enalapril	HTN	Open	470	NR	NR	58	100	NR	62	5
ACTION	2004	Nifedipine	Placebo	CAD	Double	7665	4	3	63	15	21	18	5
ALLHAT	2002	Amlodipine	Lisinopril	HTN	Double	33357	1	0.6	67	37	25	12	5
	2002	Amlodipine	Chlortalidone	HTN	Double		0.8	0.7	67	37	25	12	5
ASCOT-BPLA	2005	Amlodipine	Atenolol	HTN	Open	19257	1.8	2.1	63	27	23	33	6
CAMELOT	2004	Amlodipine	Enalapril	CAD	Double	1991	0.9	0.6	58	17	27	27	4
	2004	Amlodipine	Placebo	CAD	Double		5.8	3.1	57	17	27	27	4
CAPARES	2000	Amlodipine	Placebo	CAD	Double	635	ND	ND	56	23	19	23	0.3
CASE-J	2006	Amlodipine	Candesartan	HTN	Open	4703	1.9	0	64	43	45	NA	3
CONVINCE	2003	Verapamil	Atenolol/HCT	HTN	Double	16602	0.1	0.7	66	20	55	23	3
ELSA	2002	Lacidipine	Atenolol	HTN	Double	2334	0.2	0.1	56	NA	55	20	4
FEVER	2005	Felodipine	Placebo	HTN	Double	9711	3.3	1.3	61	11	39	29	3
IDNT	2001	Amlodipine	Irbesartan	HTN	Double	1715	0	1	59	100	NR	NR	3
	2001	Amlodipine	Placebo	HTN	Double	6321	1	0	59	100	NR	NR	3
INSIGHT	2000	Nifedipine	Co-amilozide	HTN	Double		0	0	65	21	54	28	4
INVEST	2003	Verapamil	Atenolol	CAD	PROBE	22576	0.3	0	66	28	52	46	3
JMIC-B	2004	Nifedipine	ACE	CAD	PROBE	1650	4	2	66	24	31	34	3
MOSES	2005	Nitrendipine	Eprosartan	HTN	Open	1352	2	1	68	38	46	NR	3
NICOLE	2003	Nisoldipine	Placebo	CAD	Double	819	8	3	60	11	21	71	3
NICS-EH	1999	Nicardicapine	Trichlormethiazide	HTN	Double	414	0.7	1.2	70	ND	67	9	5
NORDIL	2000	Diltiazem	Bblock/diuretics	HTN	PROBE	10881	3	0.1	60	ND	51	22	5
PRAISE	1996	Amlodipine	Placebo	HF	Double	1153	NR	NR	65	ND	24	NR	1
PREVENT	2000	Amlodipine	Placebo	CAD	Double	825	7	4	57	ND	20	25	3
SHELL	2003	Lacidipine	Chlortalidone	HTN	Open	1882	0	0	72	ND	61	15	3
STOP-2	1999	Felodipine	B Blocker /diuretic	HTN	PROBE	6614	1	1	76	11	22	66	5
	1999	Felodipine	Enalapril/Lisinopril	HTN	PROBE		0	1	76	11	22	66	5
SYST-EUR	1997	Nitrendipine	Placebo	HTN	Double	4695	9.9	5.5	70	NR	67	26	3
VALUE	2004	Amlodipine	Valsartan	HTN	Double	15245	2.1	1.7	67	NR	42	NR	4
VESPA	2004	Verapamil	Placebo	CAD	Double	700	NR	NR	60	13	18	22	1
VHAS	1997	Verapamil	Chlortalidone	CAD	Open	1414	0.6	0.4	54	NR	51	18	2

Table 3. Trials assessing CCBs (adapted from **Publication 3**). Abbreviations: CAD: Coronary Artery Disease CCB: Calcium Channel Blocker. DBP: Diastolic Blood Pressure. HCT: Hydroclorothiazide HTN: Hypertension. N: Number. NR: Not Reported. PROBE: Prospective randomized open blinded end-point. SBP: Systolic Blood Pressure
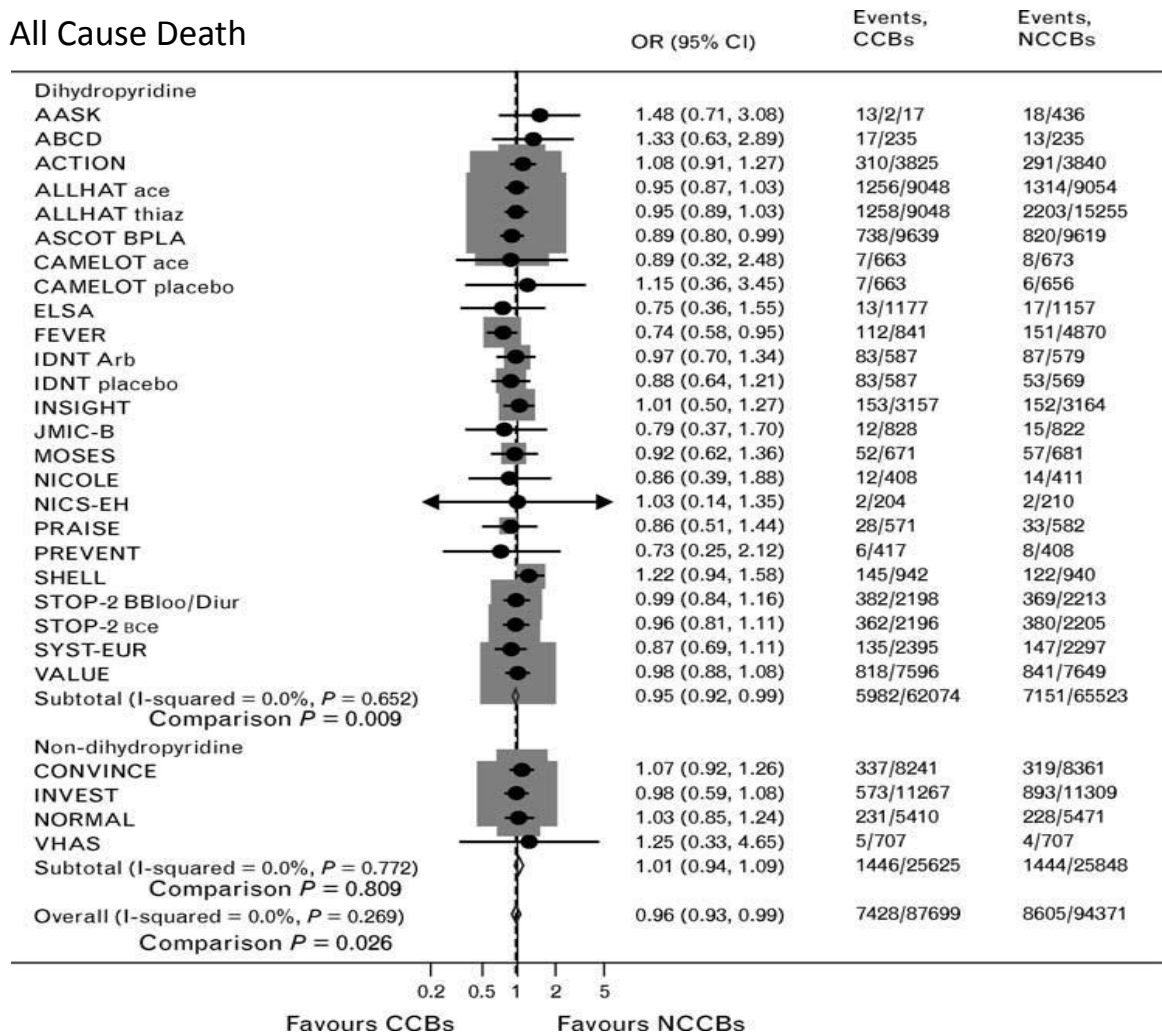
Figure 11. ORs for All Cause Death. Solid squares represent ORs in trials and have a size proportional to the number of events. The 95% CI for individual trials are denoted by lines and those for the pooled odd ratios are denoted by empty diamonds.

Overall, CCBs did not reduce the risk of fatal or nonfatal myocardial infarction (OR 1; 95% CI 0.95–1.04; p=0.83). This was true when CCBs were compared to placebo (OR 0.95; 95% CI 0.84–1.09; p=0.48) or to
ACE-Is (OR 1.08; 95% CI 0.98–1.18 p=0.1) (Figure 15).

CCBs decreased the risk of fatal or nonfatal stroke (OR 0.86; 95%

Cardiovascular Death

	OR (95% CI)	Events, CCBs	Events, NCCBs
Dihydropyridine			
ABCD	2.04 (0.69, 6.08)	10/235	5/235
ACTION	1.04 (0.83, 1.31)	154/3825	149/3840
ALLHAT ace	0.97 (0.87, 1.09)	603/9048	618/9054
ALLHAT thiaz	1.02 (0.92, 1.14)	603/9048	996/15255
ASCOT BPLA	0.76 (0.65, 0.90)	263/9639	342/9618
CAMELOT ace	1.02 (0.29, 3.52)	5/663	5/673
CAMELOT placebo	2.48 (0.48, 12.83)	5/663	2/655
ELSA	0.49 (0.15, 1.63)	4/1177	8/1157
FEVER	0.72 (0.53, 0.98)	73/4841	101/4870
INSIGHT	1.16 (0.80, 1.69)	60/3157	52/3164
JMIC-B	0.99 (0.32, 3.09)	6/828	6/822
NICS-EH	3.10 (0.13, 76.62)	1/204	0/210
STOP-2 BBloo/Diur	0.96 (0.79, 1.17)	212/2196	221/2213
STOP-2 ace	0.44 (0.77, 1.14)	212/2196	226/2205
SYST-EUR	0.74 (0.53, 1.03)	64/2398	82/2297
VALUE	1.01 (0.86, 1.18)	304/7596	304/7649
Subtotal (I-squared = 30.4%, P = 0.120)	0.95 (0.90, 1.01)	2579/577	3117/63917
Comparison P = 0.08			
Non-dihydropyridine			
CONVINCE	1.08 (0.86, 1.36)	152/8241	143/8361
INVEST	1.00 (0.88, 1.15)	431/11267	431/11309
NORMAL	1.16 (0.90, 1.49)	131/5410	115/5471
VHAS	1.25 (0.33, 4.68)	5/707	4/707
Subtotal (I-squared = 0.0%, P = 0.779)	1.05 (0.94, 1.16)	719/25625	693/25848
Comparison P = 0.0.4			
Overall (I-squared = 24.1%, P = 0.160)	0.97 (0.93, 1.02)	3298/83339	3810/89765
Comparison P = 0.24			

0.2 0.5 1 2 5

Favours CCBs   Favours NCCBs

Figure 12. ORs for Cardiovascular Death. Solid squares represent ORs in trials and have a size proportional to the number of events. The 95% CI for individual trials are denoted by lines and those for the pooled odd ratios are denoted by empty diamonds.

CI 0.82–0.90; p=0.0001). This reduced risk was observed only for dihydropyridine CCBs and not for non-dihydropyridine CCBs (OR 0.93; 95% CI 0.81–1.06; p=0.25). Interestingly, CCBs were more effective than

ACE-is to reduce stroke incidence (OR 0.87; 95% CI 0.78-0.97; p<0.05) (Figure 16).

Major Cardiovascular Events

Figure 13. ORs for Major Cardiovascular Events. Solid squares represent ORs in trials and have a size proportional to the number of events. The 95% CI for individual trials are denoted by lines and those for the pooled odd ratios are denoted by empty diamonds.

Heart Failure

	OR (95% CI)	Events, CCBs	Events, NCCBs
ACE			
ABCD	1.20 (0.36, 3.98)	6/235	5/235
ALLHAT ace	1.17 (1.04, 1.31)	706/9048	612/9054
CAMELOT ace	0.76 (0.17, 3.36)	3/663	4/673
JMIC-B	1.33 (0.56, 3.13)	12/828	9/822
STOP-2 ace	1.20 (1.02, 1.56)	186/2196	149/2205
Subtotal (I-squared = 0.0%, P = 0.925)	1.19 (1.08, 1.31)	913/12970	779/12989
Comparison P = 0.001			
Placebo			
ACTION	0.74 (0.58, 0.94)	117/3825	158/3840
CAMELOT placebo	0.60 (0.15, 2.40)	3/663	5/655
FEVER	0.67 (0.37, 1.21)	18/4841	27/4870
SYST-EUR	0.26 (0.05, 1.27)	1/417	5/408
Subtotal (I-squared = 0.0%, P = 0.775)	0.75 (0.49, 1.13)	40/2398	51/2297
Comparison P = 0.001	0.72 (0.58, 0.87)	179/12144	246/12070
Diuretic_and_orBBlocker			
ALLHAT thiaz	1.41 (1.27, 1.57)	706/9048	870/15255
ASCOT BPLA	0.84 (0.67, 1.06)	134/9639	159/9618
CONVINCE	1.28 (0.99, 1.67)	126/8241	100/8361
INSIGHT	0.14 (0.01, 1.33)	26/3157	12/3164
NICS-EH	1.14 (0.01, 1.33)	0/204	3/210
NORDIL	1.20 (0.84, 1.74)	63/5410	53/5471
SHELL	1.21 (0.66, 2.23)	23/942	19/940
STOP-2 BBloc/Diur	0.06 (0.86, 1.32)	186/2196	177/2213
VHAS	7.40 (0.46, 118.42)	2/707	0/707
Subtotal (I-squared = 70.0%, P = 0.001)	1.26 (1.16, 1.36)	1266/39544	1393/45939
Comparison P = 0.0001			
ARB			
MOSES	1.59 (1.00, 2.52)	46/671	30/681
VALUE	1.15 (0.99, 1.33)	400/7596	354/7649
Subtotal (I-squared = 42.2%, P = 0.188)	1.18 (1.03, 1.36)	446/8267	384384/8330
Comparison P = 0.02			
Overall (I-squared = 66.1%, P = 0.000)	1.17 (1.11, 1.24)	2804/72925	2802/79328
Comparison P = 0.0001			

0.2   0.5   1   2   5

Favours CCBs   Favours NCCBs

Figure 14. ORs for Heart Failure. Solid squares represent ORs in trials and have a size proportional to the number of events. The 95% CI for individual trials are denoted by lines and those for the pooled odd ratios are denoted by empty diamonds.

MI

|	OR (95% CI)	Events, CCBs	Events, NCCBs
ACE			
ABCD	4.14 (1.98, 8.67)	25/235	5/235
ALLHAT ace	1.00 (0.91, 1.11)	798/9048	796/9048
CAMELOT ace	1.30 (0.59, 2.86)	14/663	11/673
JMIC-B	1.23 (0.59, 2.55)	16/828	13/822
STOP-2 ace	1.32 (1.05, 1.65)	179/2196	139/2205
Subtotal (I-squared = 77.7%, P = 0.001)	1.08 (0.98, 1.18)	1032/12970	964/12989
Comparison P = 0.1			
Placebo			
ACTION	1.09 (0.93, 1.29)	320/3825	296/3840
CAMELOT placebo	0.72 (0.36, 1.44)	14/663	19/655
FEVER	0.72 (0.53, 0.97)	71/4841	99/4870
NICOLE	1.25 (0.60, 2.62)	16/408	13/411
PRAISE	0.71 (0.27, 1.86)	7/571	10/582
PREVENT	0.93 (0.49, 1.76)	19/417	20/408
SYST-EUR	0.73 (0.47, 1.13)	36/2398	47/2297
Subtotal (I-squared = 32.4%, P = 0.181)	0.95 (0.84, 1.09)	483/13123	504/13063
Comparison P = 0.48			
Diuretic_and_orBBlocker			
ALLHAT thiaz	0.99 (0.90, 1.08)	798/9048	136/15255
ASCOT BPLA	0.90 (0.80, 1.03)	469/9639	515/9618
CONVINCE	0.81 (0.64, 1.02)	133/8241	166/8361
ELSA	1.04 (0.53, 2.03)	18/1177	17/1157
INSIGHT	1.27 (0.91, 1.78)	77/3157	61/3164
INVEST	0.99 (0.79, 1.24)	151/11267	153/11309
NICS-EH	1.03 (0.14, 7.36)	2/204	2/210
NORDIL	1.18 (0.95, 1.47)	183/5410	157/5470
SHELL	0.85 (0.39, 1.85)	12/942	14/940
STOP-2 BBloc/Diur	1.19 (0.95, 1.48)	179/2196	154/2213
VHAS	0.89 (0.34, 2.31)	8/707	9/707
Subtotal (I-squared = 19.0%, P = 0.263)	0.99 (0.93, 1.05)	2030/51988	2610/58405
Comparison P = 0.72			
ARB			
CASE-J	1.06 (0.55, 2.06)	18/2349	17/2354
MOSES	1.27 (0.82, 1.96)	48/671	39/681
VALUE	0.85 (0.73, 0.99)	313/7596	369/7649
Subtotal (I-squared = 37.2%, P = 0.2.3)	0.89 (0.78, 1.03)	379/10616	425/10684
Comparison P = 0.12			
Overall (I-squared = 47.8%, P = 0.004)	1.00 (0.95, 1.04)	3924/88697	4503/95141
Comparison P = 0.83			

0.2   0.5   1   2   5

Favours CCBs   Favours NCCBs

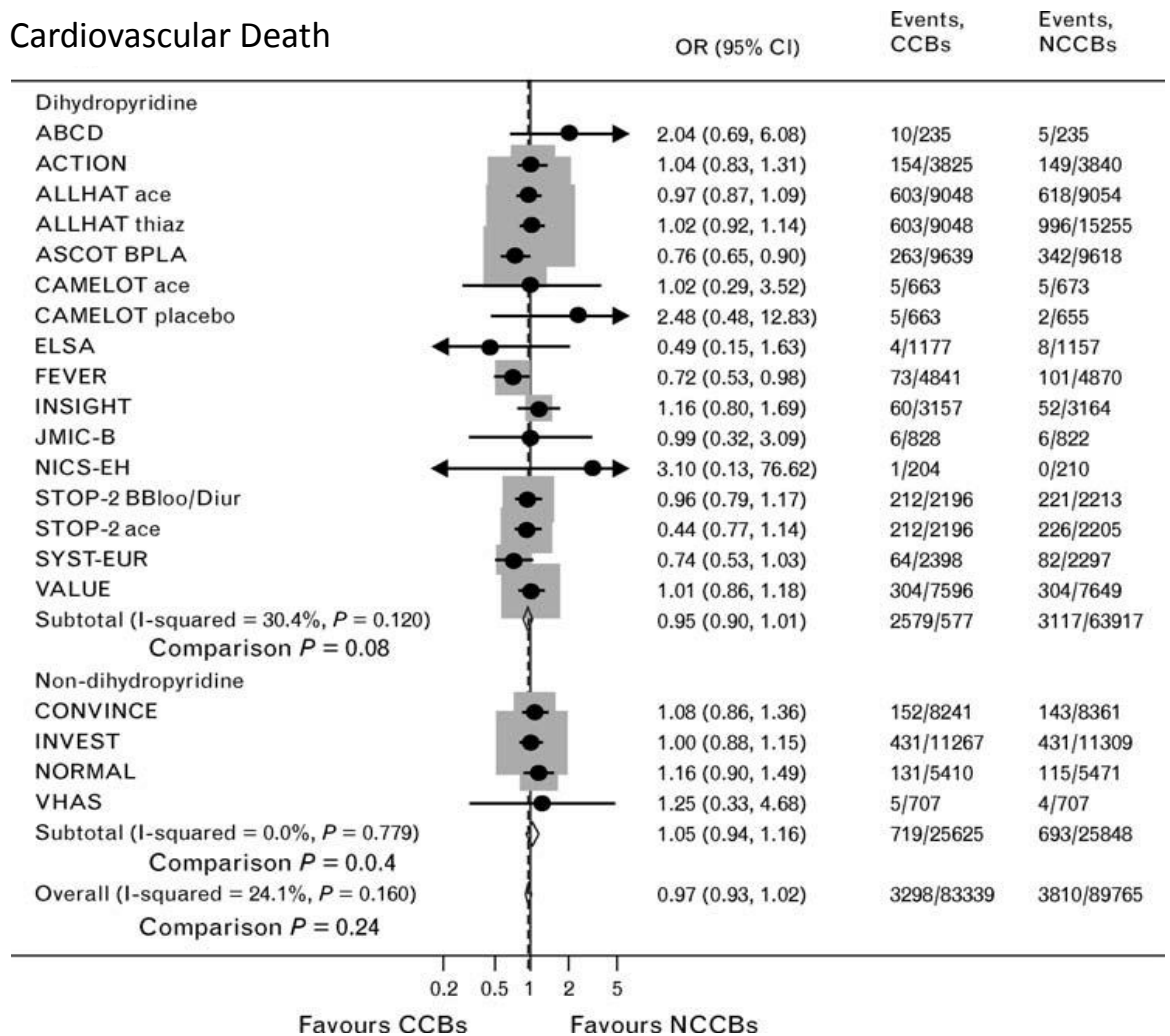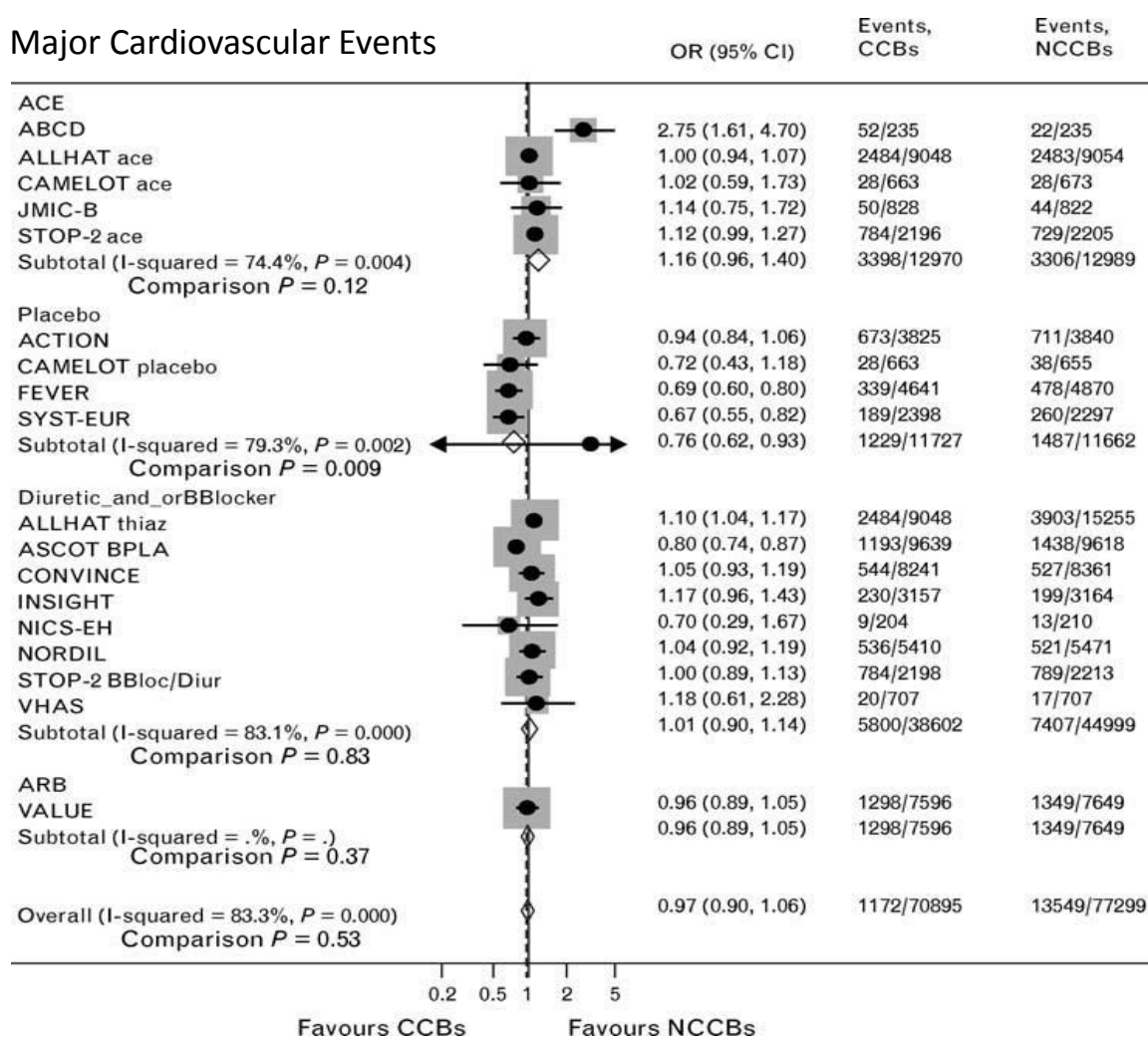**Figure 15.** ORs for MI. Solid squares represent ORs in trials and have a size proportional to the number of events. The 95% CI for individual trials are denoted by lines and those for the pooled odd ratios are denoted by empty diamonds.

Stroke

	OR (95% CI)	Events, CCBs	Events, NCCBs
ACE			
ABCD	1.59 (0.62, 4.06)	11/235	7/235
ALLHAT ace	0.82 (0.71, 0.94)	377/9048	457/9054
CAMELOT ace	0.76 (0.27, 2.18)	6/663	8/673
JMIC-B	0.99 (0.49, 2.00)	16/828	16/822
STOP-2 ace	0.96 (0.79, 1.18)	207/2196	215/2205
Subtotal (I-squared = 0.0%, P = 0.479)	0.87 (0.78, 0.97)	617/12970	703/12989
Comparison P = 0.016			
Placebo			
ACTION	0.76 (0.57, 1.01)	82/3825	108/3840
CAMELOT placebo	0.50 (0.20, 1.27)	6/663	12/655
FEVER	0.70 (0.58, 0.85)	177/4841	25/4870
NICOLE	0.58 (0.18, 1.90)	4/408	7/411
PREVENT	0.98 (0.28, 3.40)	5/417	5/408
SYST-EUR	0.58 (0.41, 0.83)	49/2398	80/2297
Subtotal (I-squared = 0.0%, P = 0.829)	0.73 (0.47, 1.13)	323/12552	463/12481
Comparison P = 0.0001			
Diuretic_and_orBBlocker			
ALLHAT thiaz	0.94 (0.83, 1.07)	377/9048	675/15255
ASCOT BPLA	0.77 (0.66, 0.89)	327/9639	422/9618
CONVINCE	1.15 (0.89, 1.47)	133/8241	118/8361
ELSA	0.63 (0.28, 1.44)	9/1177	14/1157
INSIGHT	0.91 (0.65, 1.26)	67/3157	74/3164
INVEST	0.89 (0.70, 1.12)	131/11267	148/11309
NICS-EH	0.77 (0.26, 2.22)	6/204	8/210
NORDIL	0.82 (0.66, 1.01)	159/5410	196/5470
SHELL	0.97 (0.61, 1.54)	37/942	38/940
STOP-2 BBloc/Diur	0.87 (0.71, 1.06)	207/2196	237/2213
VHAS	1.25 (0.34, 4.64)	5/707	4/707
Subtotal (I-squared = 4.1%, P = 0.403)	0.88 (0.82, 0.94)	1458/51988	1934/58405
Comparison P = 0.0001			
ARB			
CASE-J	1.29 (0.88, 1.89)	60/2349	47/2354
MOSES	1.20 (0.76, 1.89)	42/671	36/681
VALUE	0.87 (0.74, 1.03)	281/7596	322/7649
Subtotal (I-squared = 54.1%, P = 0.113)	0.95 (0.82, 1.10)	383/10616	405/10684
Comparison P = 0.48			
Overall (I-squared = 25.4%, P = 0.123)	0.86 (0.82, 0.90)	278/88126	3505/94559
Comparison P = 0.0001			

0.2 0.5 1 2 5

Favours CCBs   Favours NCCBs

Figure 16. ORs for stroke. Solid squares represent ORs in trials and have a size proportional to the number of events. The 95% CI for individual trials are denoted by lines and those for the pooled odd ratios are denoted by empty diamonds.
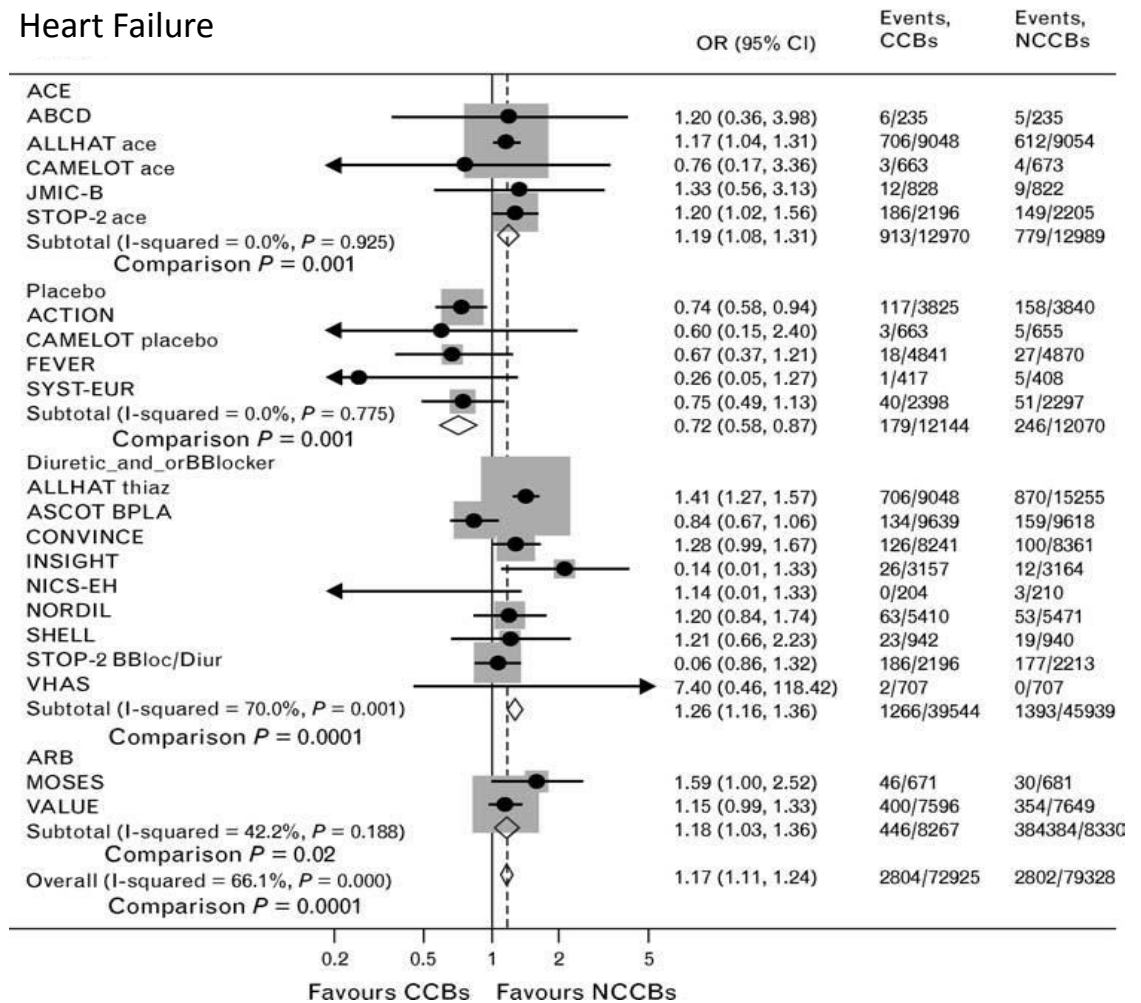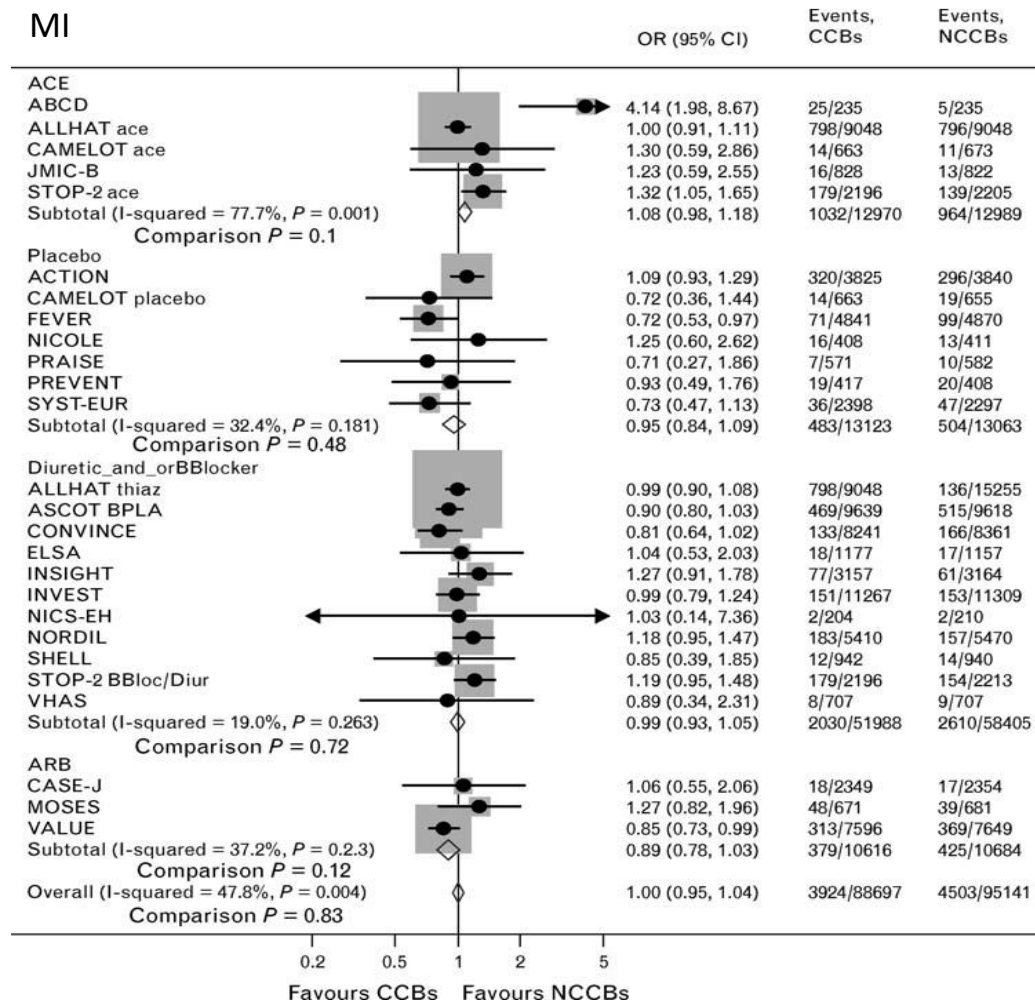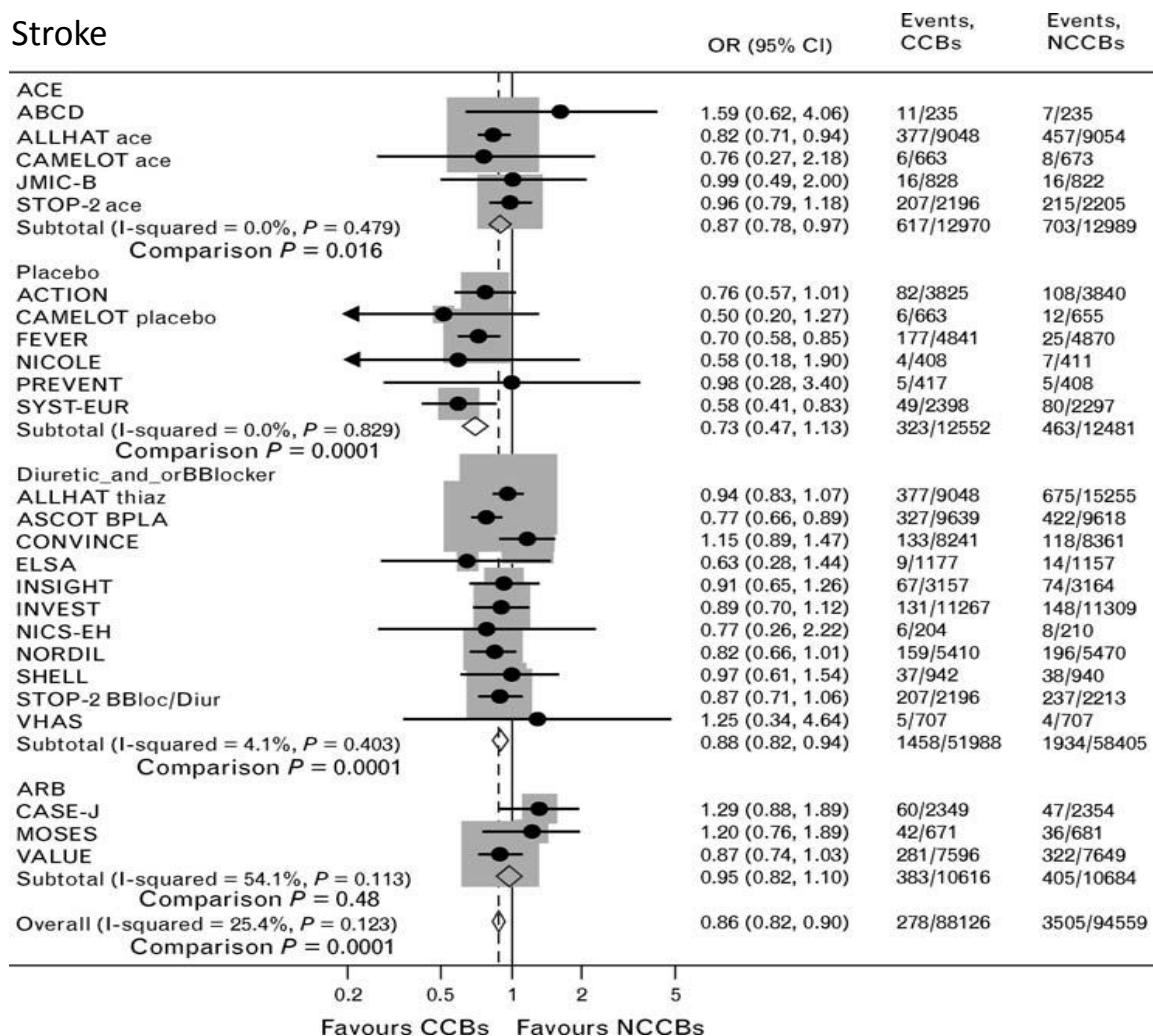
As per further sensitivity analysis, a meta-regression was performed with potential effect modifiers as mean age, sex, smoking, CHD at baseline, heart failure, at baseline, between-group achieved difference in systolic and diastolic blood pressure and Detsky quality score (122). The most significant result was that the favorable outcome provided by CCBs was driven by the blood pressure reduction. For 1mmHg systolic blood pressure reduction there was a 4% reduction in major cardiovascular events, 6% reduction in heart failure and 4% reduction in stroke during the study duration (Figure 17).
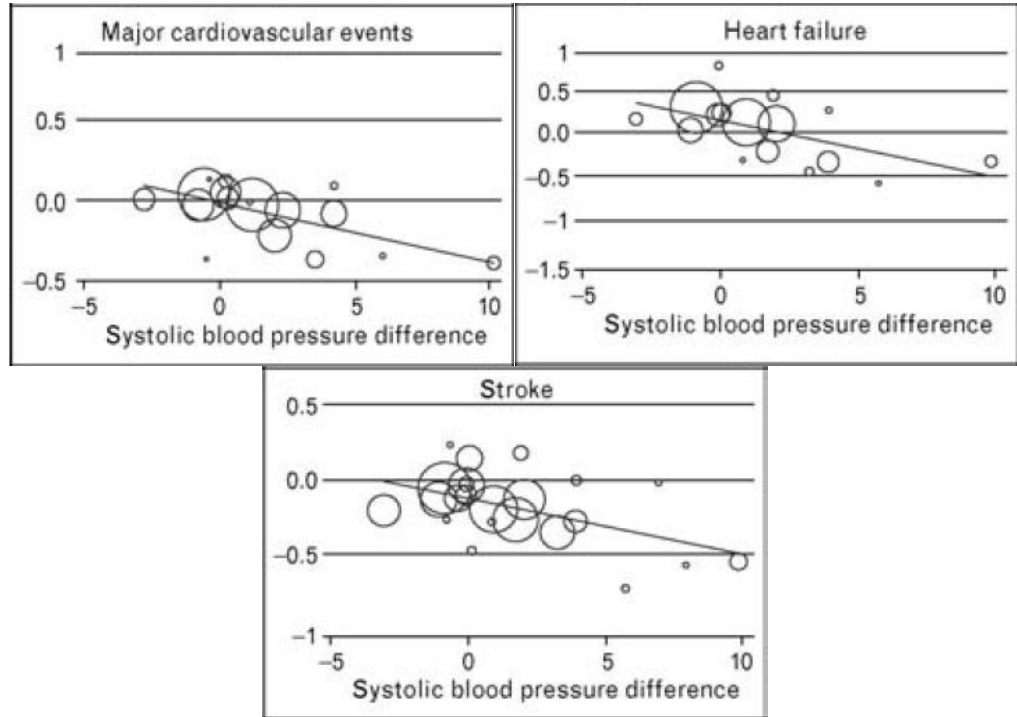
Figure 17. Meta-regression analysis between achieved difference in systolic blood pressure (mmHg) and all outcomes. Logs of ORs are reported in the y axis and covariates in the x axis. Circles represent trials and have a size proportional to the number of events

Major Cardiovascular Events OR 0.96; 95% CI 0.94-0.98; Tau -3.88 p<0.001.
Heart Failure OR 0.94; 95% CI 0.90-0.98; Tau -3.2; p<0.01.
Stroke OR 0.96; 95% CI 0.94-0.99; Tau -3; p<0.01.

Amongst all the outcomes, a publication bias was found only for myocardial infarction (p<0.05) therefore results for this outcome must be taken cautiously.

The role of ARBs compared to ACE-Is in patients without heart failure

ACE-Is or ARBs therapy in patients without heart failure was analyzed in
26 trials included. Of 108,212 patients, a total of 53,791 were enrolled in ACE-I trials and 54,421 in ARB trials. Duration of follow-up ranged from 2 to 6.5 years (mean 3.7±1.1 years). The overall mean age of subjects was 58±11 years and 35% were women (Table 4).

ARBs significantly reduced the risk of the composite outcome compared with placebo (OR 0.92; 95% CI 0.87-0.97; p<0.01) (Figure 18).
However, by assessing outcome individually ARBs did not reduce the risk of cardiovascular death (OR 1; 95% CI 0.85-1.26, p=0.75) or MI (OR 0.9 95% CI 0.8-1, p=0.09) (both Figure 19), or all-cause death (OR 1 95% CI: 0.94-1.07; p=0.87) (Figure 18) or new-onset HF (OR 0.89; 95% CI 0.76-1.05) p=0.16 (Figure 20)

ARBs significantly reduced the risk of stroke OR 0.9 95% CI 0.83 to 0.98; p<0.05) (Figure 20) and new-onset DM (OR 0.85 95% CI 0.8-0.91; p<0.001) (Figure 21)

Of relevance, ACE-Is outperformed ARBs in all outcomes but cardiovascular death, where they exhibited similar effect (see Figures 18-21). Age, gender, body mass index, coronary artery disease, diabetes mellitus, hypertension, systolic blood pressure differences from baseline to follow up end, follow-up length and quality of trials did not significantly affect the results

No publication bias was found for any of the outcomes by applying Begg or Egger or modified Macaskill test.

Agent	Trial	Year	Treatment	Treatment (n)	Placebo (n)	Follow-up (yrs)	Age (yrs)	Women (%)	HTN (%)	DM (n)	Detsky Quality Score	CAD (%)
ARBs	DIRECT-PREVENT-1	2008	Candesartan	711	710	4.7	30	44	0	100	19	0
	DIRECT-PROTECT-1	2008	Candesartan	951	954	4.8	32	43	0	100	19	0
	DIRECT-PROTECT-2	2008	Candesartan	951	954	4.7	57	50	62	100	19	0
	IDNT	2003	Irbesartan	579	567	2.6	59	32	100	100	20	28
	IRMA-2	2001	Irbesartan	404	207	2	58	31	100	100	20	8
	Kondo et al.	2003	Candesartan	203	203	2	65	24	44	25	17	100
	NAVIGATOR	2010	Valsartan	4631	4675	6.5	64	51	78	0	21	28
	ORIENT	2011	Olmesartan	282	284	3.2	59	69	94	100	17	8
	PROFESS	2008	Telmisartan	10146	10186	2.5	66	36	74	28	20	NA
	RENAAL	2001	Losartan	751	762	3.4	60	37	94	100	19	21
	ROADMAP	2011	Olmesartan	2232	2215	3.2	58	54	NA	100	20	31
	SCOPE	2003	Candesartan	2477	2460	3.7	76	65	53	12	18	5
	TRANSCEND	2008	Telmisartan	2954	2972	4.67	67	43	76	36	20	75
ACE-Is	AIPRI	1996	Benazepril	300	283	3	51	28	82	NA	16	NA
	CAMELOT	2004	Enalapril	673	655	2	58	28	60	19	19	100
	DIABHYCAR	2004	Ramipril	2443	2469	4	65	30	56	100	18	6
	DREAM	2006	Ramipril	2623	2646	3	55	59	44	0	18	NA
	EUROPA	2003	Perindopril	6110	6108	4.2	60	15	27	12	20	100
	HOPE	2000	Ramipril	4645	4652	5	66	27	47	39	20	80
	IMAGINE	2007	Quinapril	1280	1273	2.95	61	13	47	9	21	100
	Lewis et al	1993	Captopril	207	202	3	35	47	76	100	16	NA
	PART-2	2000	Ramipril	308	309	4.7	61	18	NA	9	18	100
	PEACE	2004	Trandolapril	4158	4132	4.8	64	18	46	17	20	100
	PROGRESS	2001	Perindopril	3051	3054	4	64	30	48	13	19	8
	QUIET	2001	Quinapril	878	872	3	58	18	47	16	18	100
	SCAT	2000	Enalapril	229	231	3.98	62	11	36	11	17	100

Table 4. Trials assessing ACEs and ARBs (adapted from **Publication 4**). Abbreviations: ACE-ARBs as per manuscript. CAD: Coronary Artery Disease HTN: Hypertension. n: Number. NA: Available. Yrs: years.
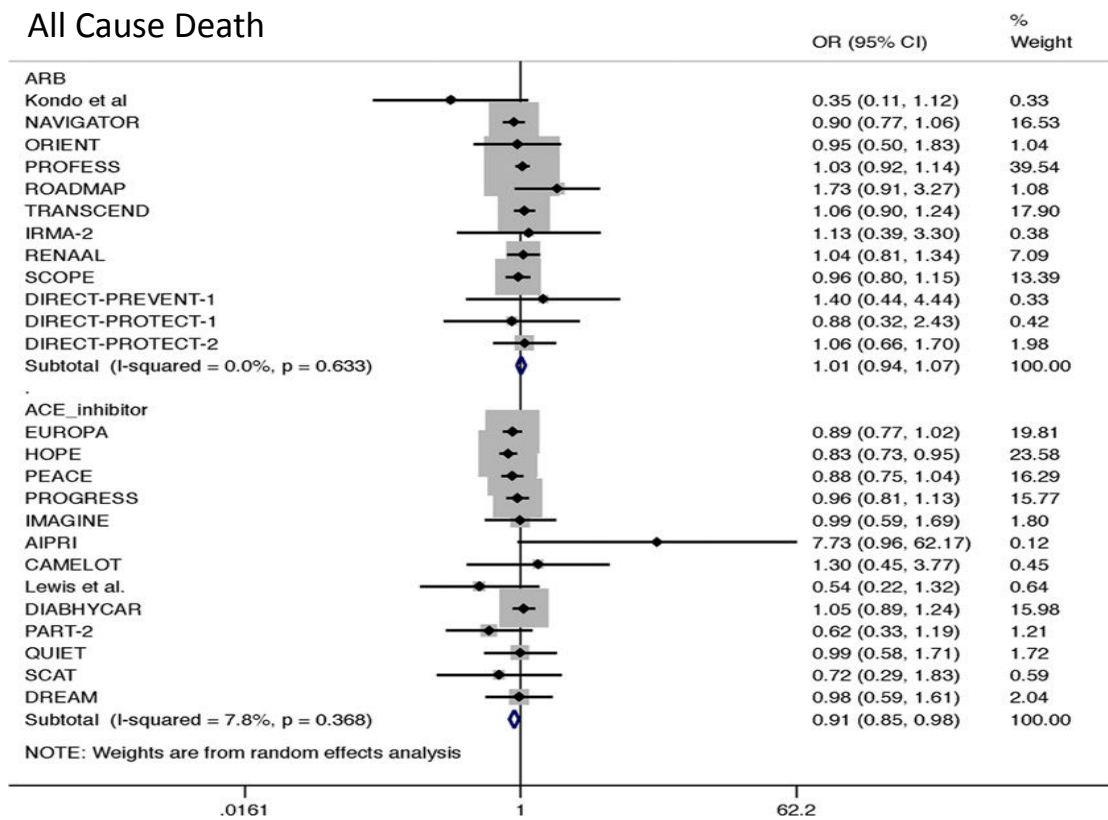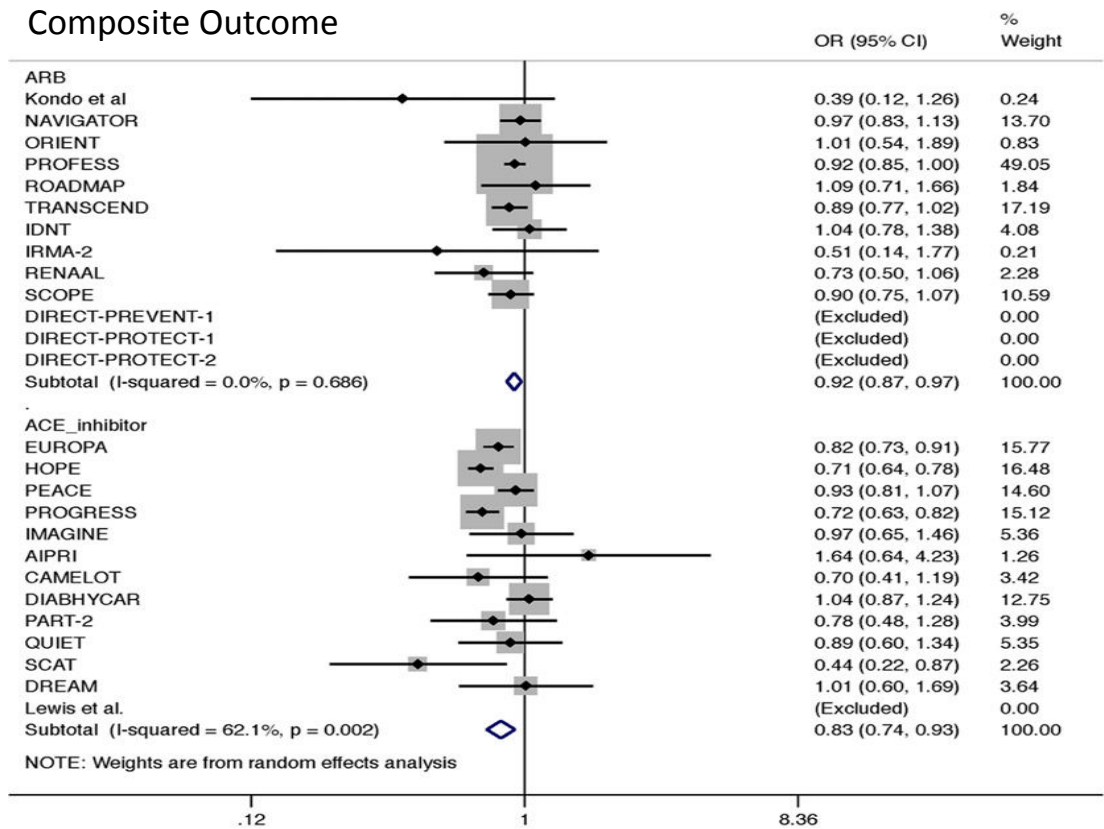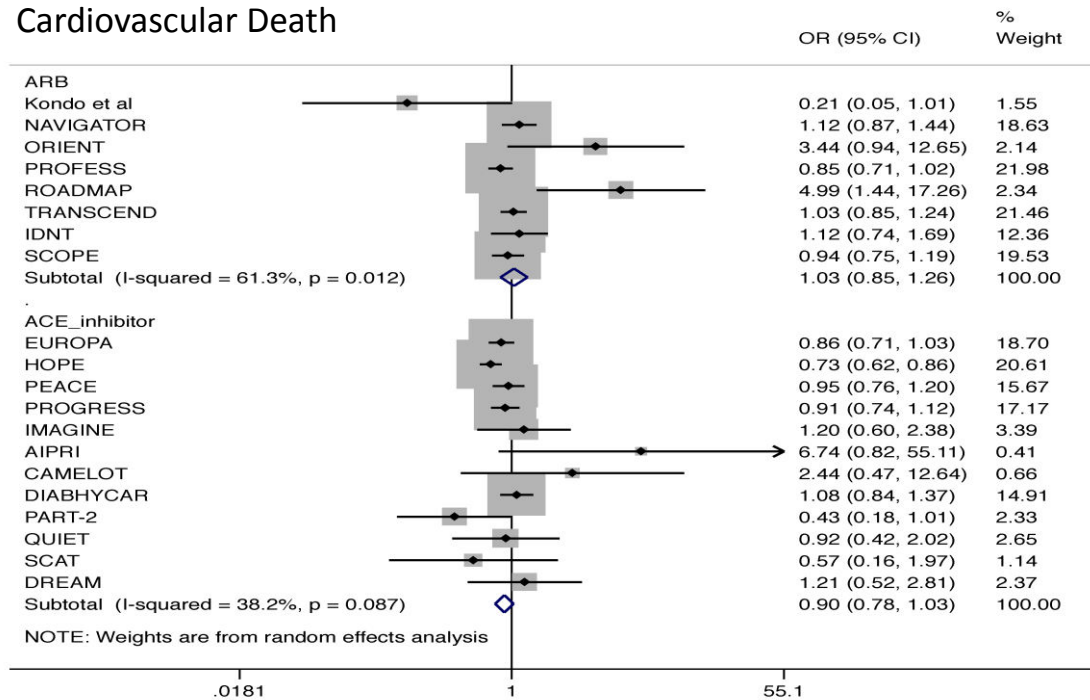
Composite Outcome

	OR (95% CI)	% Weight
ARB		
Kondo et al	0.39 (0.12, 1.26)	0.24
NAVIGATOR	0.97 (0.83, 1.13)	13.70
ORIENT	1.01 (0.54, 1.89)	0.83
PROFESS	0.92 (0.85, 1.00)	49.05
ROADMAP	1.09 (0.71, 1.66)	1.84
TRANSCEND	0.89 (0.77, 1.02)	17.19
IDNT	1.04 (0.78, 1.38)	4.08
IRMA-2	0.51 (0.14, 1.77)	0.21
RENAAL	0.73 (0.50, 1.06)	2.28
SCOPE	0.90 (0.75, 1.07)	10.59
DIRECT-PREVENT-1	(Excluded)	0.00
DIRECT-PROTECT-1	(Excluded)	0.00
DIRECT-PROTECT-2	(Excluded)	0.00
Subtotal (I-squared = 0.0%, p = 0.686)	0.92 (0.87, 0.97)	100.00
ACE_inhibitor		
EUROPA	0.82 (0.73, 0.91)	15.77
HOPE	0.71 (0.64, 0.78)	16.48
PEACE	0.93 (0.81, 1.07)	14.60
PROGRESS	0.72 (0.63, 0.82)	15.12
IMAGINE	0.97 (0.65, 1.46)	5.36
AIPRI	1.64 (0.64, 4.23)	1.26
CAMELOT	0.70 (0.41, 1.19)	3.42
DIABHYCAR	1.04 (0.87, 1.24)	12.75
PART-2	0.78 (0.48, 1.28)	3.99
QUIET	0.89 (0.60, 1.34)	5.35
SCAT	0.44 (0.22, 0.87)	2.26
DREAM	1.01 (0.60, 1.69)	3.64
Lewis et al.	(Excluded)	0.00
Subtotal (I-squared = 62.1%, p = 0.002)	0.83 (0.74, 0.93)	100.00

NOTE: Weights are from random effects analysis

.12   1   8.36

All Cause Death

	OR (95% CI)	% Weight
ARB		
Kondo et al	0.35 (0.11, 1.12)	0.33
NAVIGATOR	0.90 (0.77, 1.06)	16.53
ORIENT	0.95 (0.50, 1.83)	1.04
PROFESS	1.03 (0.92, 1.14)	39.54
ROADMAP	1.73 (0.91, 3.27)	1.08
TRANSCEND	1.06 (0.90, 1.24)	17.90
IRMA-2	1.13 (0.39, 3.30)	0.38
RENAAL	1.04 (0.81, 1.34)	7.09
SCOPE	0.96 (0.80, 1.15)	13.39
DIRECT-PREVENT-1	1.40 (0.44, 4.44)	0.33
DIRECT-PROTECT-1	0.88 (0.32, 2.43)	0.42
DIRECT-PROTECT-2	1.06 (0.66, 1.70)	1.98
Subtotal (I-squared = 0.0%, p = 0.633)	1.01 (0.94, 1.07)	100.00
ACE_inhibitor		
EUROPA	0.89 (0.77, 1.02)	19.81
HOPE	0.83 (0.73, 0.95)	23.58
PEACE	0.88 (0.75, 1.04)	16.29
PROGRESS	0.96 (0.81, 1.13)	15.77
IMAGINE	0.99 (0.59, 1.69)	1.80
AIPRI	7.73 (0.96, 62.17)	0.12
CAMELOT	1.30 (0.45, 3.77)	0.45
Lewis et al.	0.54 (0.22, 1.32)	0.64
DIABHYCAR	1.05 (0.89, 1.24)	15.98
PART-2	0.62 (0.33, 1.19)	1.21
QUIET	0.99 (0.58, 1.71)	1.72
SCAT	0.72 (0.29, 1.83)	0.59
DREAM	0.98 (0.59, 1.61)	2.04
Subtotal (I-squared = 7.8%, p = 0.368)	0.91 (0.85, 0.98)	100.00

NOTE: Weights are from random effects analysis

.0161   1   62.2

Figure 18. ORs for composite outcome (top) and all cause death (bottom). Solid squares represent ORs in trials and have a size proportional to the number of events. 95% CI for individual trials are denoted by lines and those for the pooled
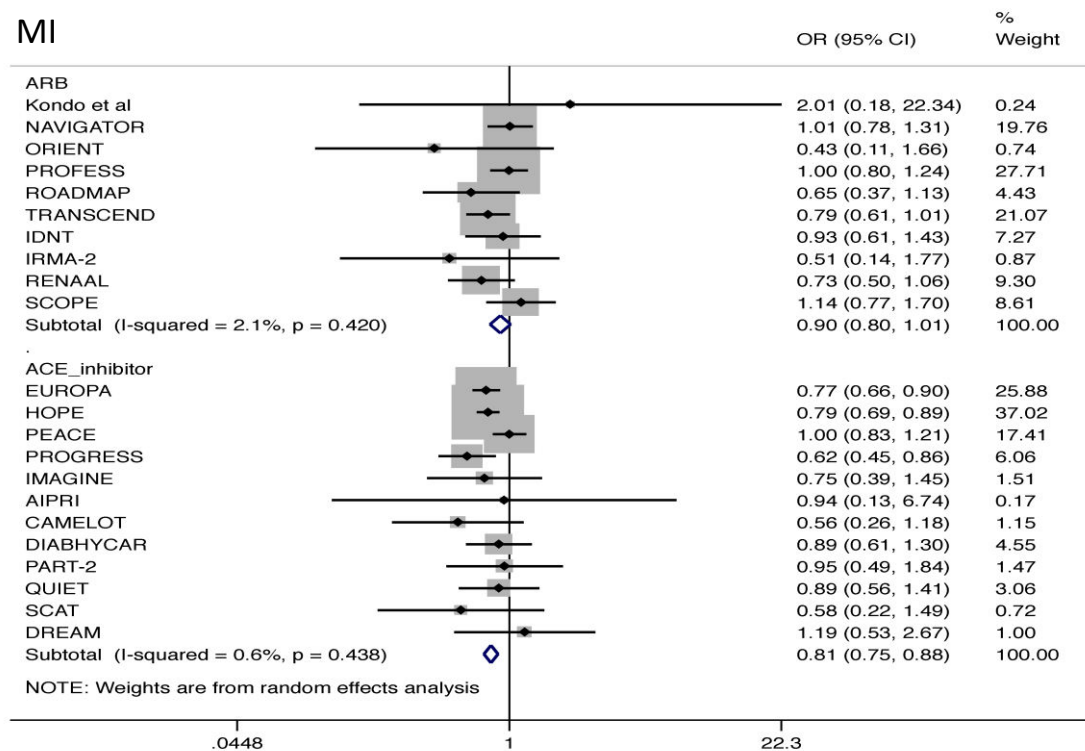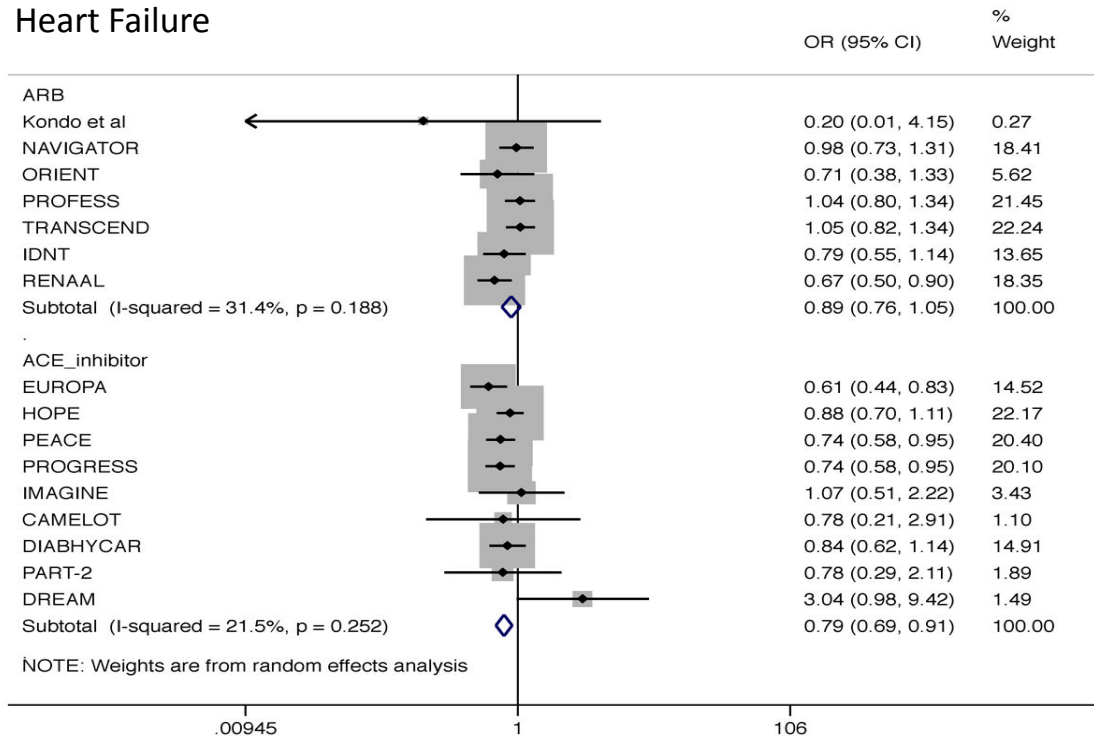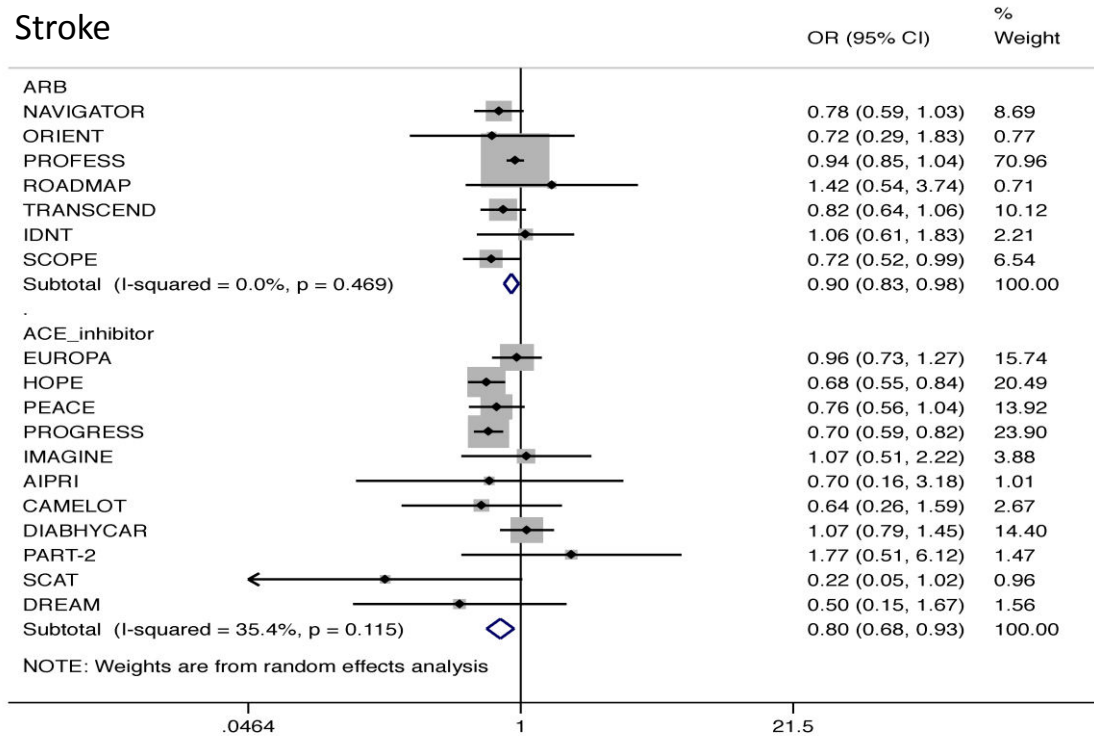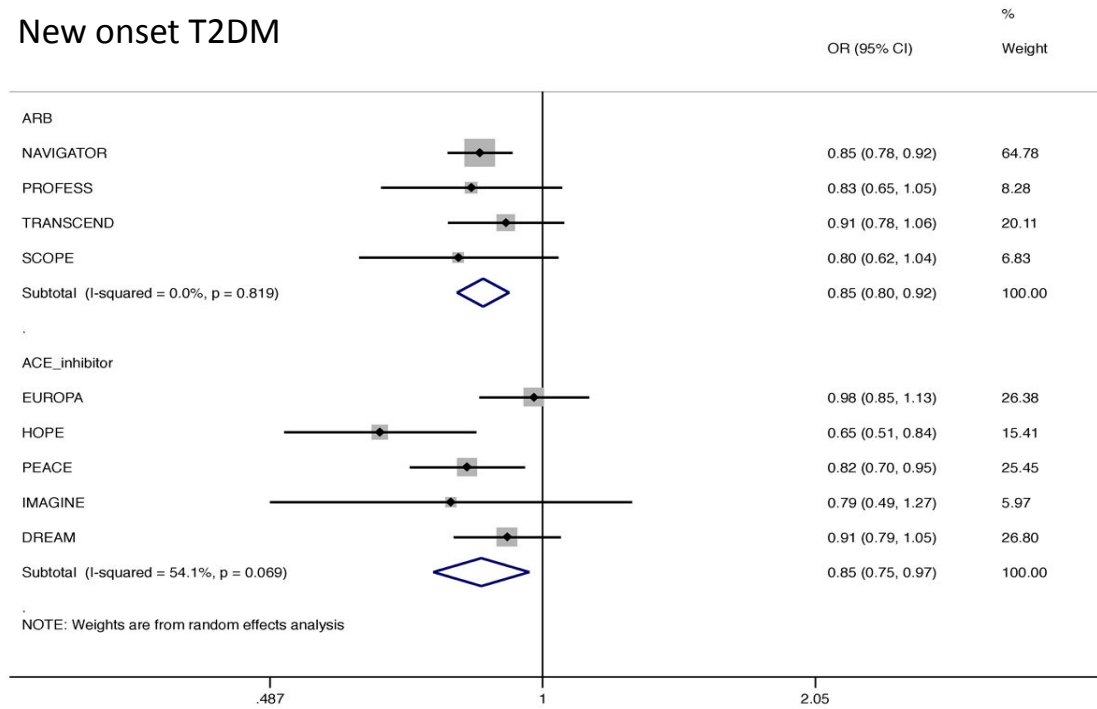
ORs by empty diamonds.

Cardiovascular Death

	OR (95% CI)	% Weight
ARB		
Kondo et al	0.21 (0.05, 1.01)	1.55
NAVIGATOR	1.12 (0.87, 1.44)	18.63
ORIENT	3.44 (0.94, 12.65)	2.14
PROFESS	0.85 (0.71, 1.02)	21.98
ROADMAP	4.99 (1.44, 17.26)	2.34
TRANSCEND	1.03 (0.85, 1.24)	21.46
IDNT	1.12 (0.74, 1.69)	12.36
SCOPE	0.94 (0.75, 1.19)	19.53
Subtotal (I-squared = 61.3%, p = 0.012)	1.03 (0.85, 1.26)	100.00
ACE_inhibitor		
EUROPA	0.86 (0.71, 1.03)	18.70
HOPE	0.73 (0.62, 0.86)	20.61
PEACE	0.95 (0.76, 1.20)	15.67
PROGRESS	0.91 (0.74, 1.12)	17.17
IMAGINE	1.20 (0.60, 2.38)	3.39
AIPRI	6.74 (0.82, 55.11)	0.41
CAMELOT	2.44 (0.47, 12.64)	0.66
DIABHYCAR	1.08 (0.84, 1.37)	14.91
PART-2	0.43 (0.18, 1.01)	2.33
QUIET	0.92 (0.42, 2.02)	2.65
SCAT	0.57 (0.16, 1.97)	1.14
DREAM	1.21 (0.52, 2.81)	2.37
Subtotal (I-squared = 38.2%, p = 0.087)	0.90 (0.78, 1.03)	100.00

NOTE: Weights are from random effects analysis

.0181 — 1 — 55.1

MI

	OR (95% CI)	% Weight
ARB		
Kondo et al	2.01 (0.18, 22.34)	0.24
NAVIGATOR	1.01 (0.78, 1.31)	19.76
ORIENT	0.43 (0.11, 1.66)	0.74
PROFESS	1.00 (0.80, 1.24)	27.71
ROADMAP	0.65 (0.37, 1.13)	4.43
TRANSCEND	0.79 (0.61, 1.01)	21.07
IDNT	0.93 (0.61, 1.43)	7.27
IRMA-2	0.51 (0.14, 1.77)	0.87
RENAAL	0.73 (0.50, 1.06)	9.30
SCOPE	1.14 (0.77, 1.70)	8.61
Subtotal (I-squared = 2.1%, p = 0.420)	0.90 (0.80, 1.01)	100.00
ACE_inhibitor		
EUROPA	0.77 (0.66, 0.90)	25.88
HOPE	0.79 (0.69, 0.89)	37.02
PEACE	1.00 (0.83, 1.21)	17.41
PROGRESS	0.62 (0.45, 0.86)	6.06
IMAGINE	0.75 (0.39, 1.45)	1.51
AIPRI	0.94 (0.13, 6.74)	0.17
CAMELOT	0.56 (0.26, 1.18)	1.15
DIABHYCAR	0.89 (0.61, 1.30)	4.55
PART-2	0.95 (0.49, 1.84)	1.47
QUIET	0.89 (0.56, 1.41)	3.06
SCAT	0.58 (0.22, 1.49)	0.72
DREAM	1.19 (0.53, 2.67)	1.00
Subtotal (I-squared = 0.6%, p = 0.438)	0.81 (0.75, 0.88)	100.00

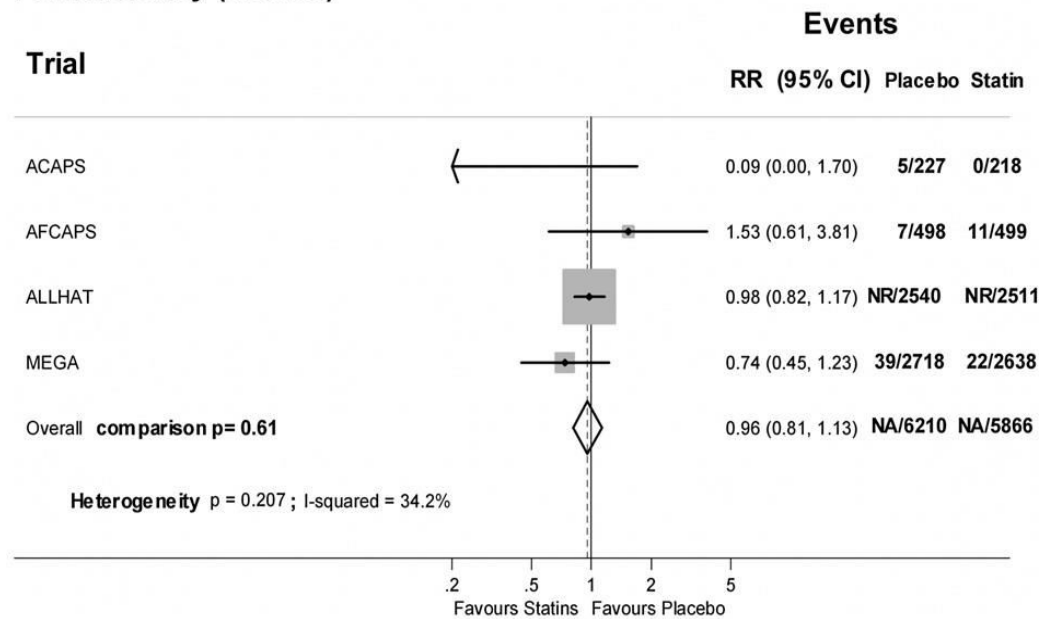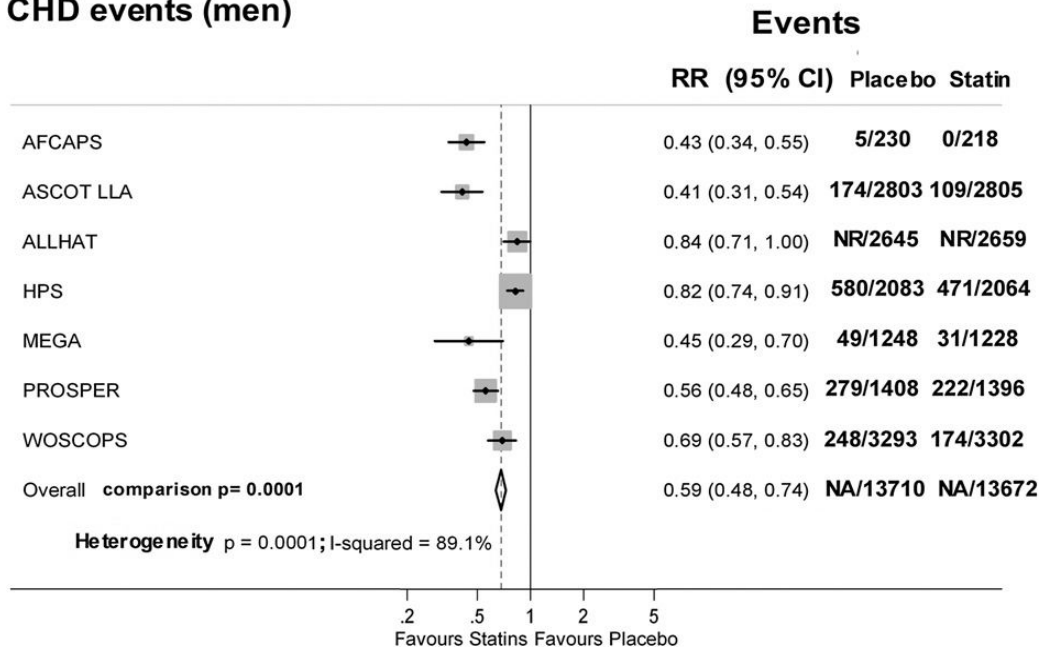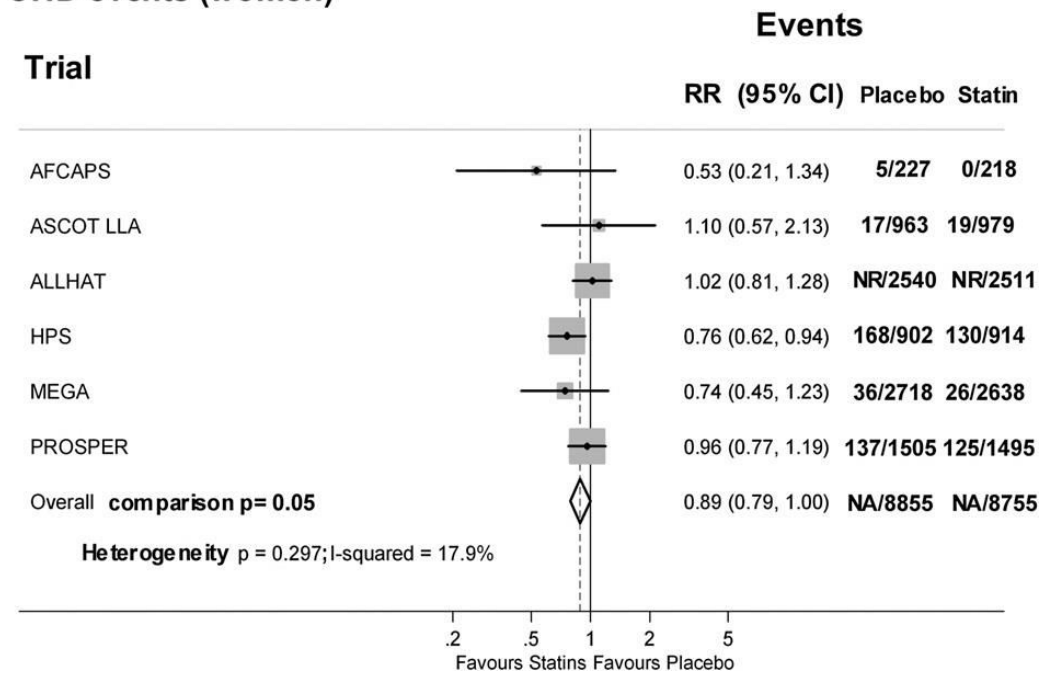NOTE: Weights are from random effects analysis

.0448 — 1 — 22.3

Figure 19. ORs for cardiovascular death (top) and MI (bottom). Solid squares represent ORs in trials and have a size proportional to the number of events. 95% CI for individual trials are denoted by lines and those for the pooled ORs by empty diamonds.

Heart Failure

	OR (95% CI)	% Weight
ARB		
Kondo et al	0.20 (0.01, 4.15)	0.27
NAVIGATOR	0.98 (0.73, 1.31)	18.41
ORIENT	0.71 (0.38, 1.33)	5.62
PROFESS	1.04 (0.80, 1.34)	21.45
TRANSCEND	1.05 (0.82, 1.34)	22.24
IDNT	0.79 (0.55, 1.14)	13.65
RENAAL	0.67 (0.50, 0.90)	18.35
Subtotal (I-squared = 31.4%, p = 0.188)	0.89 (0.76, 1.05)	100.00
.		
ACE_inhibitor		
EUROPA	0.61 (0.44, 0.83)	14.52
HOPE	0.88 (0.70, 1.11)	22.17
PEACE	0.74 (0.58, 0.95)	20.40
PROGRESS	0.74 (0.58, 0.95)	20.10
IMAGINE	1.07 (0.51, 2.22)	3.43
CAMELOT	0.78 (0.21, 2.91)	1.10
DIABHYCAR	0.84 (0.62, 1.14)	14.91
PART-2	0.78 (0.29, 2.11)	1.89
DREAM	3.04 (0.98, 9.42)	1.49
Subtotal (I-squared = 21.5%, p = 0.252)	0.79 (0.69, 0.91)	100.00

NOTE: Weights are from random effects analysis

.00945 — 1 — 106

Stroke

	OR (95% CI)	% Weight
ARB		
NAVIGATOR	0.78 (0.59, 1.03)	8.69
ORIENT	0.72 (0.29, 1.83)	0.77
PROFESS	0.94 (0.85, 1.04)	70.96
ROADMAP	1.42 (0.54, 3.74)	0.71
TRANSCEND	0.82 (0.64, 1.06)	10.12
IDNT	1.06 (0.61, 1.83)	2.21
SCOPE	0.72 (0.52, 0.99)	6.54
Subtotal (I-squared = 0.0%, p = 0.469)	0.90 (0.83, 0.98)	100.00
.		
ACE_inhibitor		
EUROPA	0.96 (0.73, 1.27)	15.74
HOPE	0.68 (0.55, 0.84)	20.49
PEACE	0.76 (0.56, 1.04)	13.92
PROGRESS	0.70 (0.59, 0.82)	23.90
IMAGINE	1.07 (0.51, 2.22)	3.88
AIPRI	0.70 (0.16, 3.18)	1.01
CAMELOT	0.64 (0.26, 1.59)	2.67
DIABHYCAR	1.07 (0.79, 1.45)	14.40
PART-2	1.77 (0.51, 6.12)	1.47
SCAT	0.22 (0.05, 1.02)	0.96
DREAM	0.50 (0.15, 1.67)	1.56
Subtotal (I-squared = 35.4%, p = 0.115)	0.80 (0.68, 0.93)	100.00

NOTE: Weights are from random effects analysis

.0464 — 1 — 21.5

Figure 20. ORs for heart failure (top) and stroke (bottom). Solid squares represent ORs in trials and have a size proportional to the number of events. 95% CI for individual trials are denoted by lines and those for the pooled ORs by empty diamonds.

Figure 21. ORs for new onset type 2 diabetes mellitus. Solid squares represent ORs in trials and have a size proportional to the number of events. 95% CI for individual trials are denoted by lines and those for the pooled ORs by empty diamonds.

The efficacy of statin therapy for primary cardiovascular prevention in women

The efficacy of statin therapy in primary prevention according to male or female gender was assessed in 8 randomized clinical trials.
Of 12 identified studies 4 studies were excluded (138-141) since we did not manage to obtain sex specific data on outcomes, despite principal investigators were contacted. Therefore 8 studies were included (83,116, 133, 134, 142-145). The total number of women included in the trials was 19,052 (and 30,194 men). Duration of treatment ranged from 2.3 to 5.3 years and averaged 3.9 years.

Statins in primary prevention did not reduce the risk of all cause mortality in both men OR 0.93; 95% CI 0.83-1.04; p=0.22 or women OR 0.96; 95% 0.81-1.13 p=0.61) (Figure 22).

Statins reduced the risk of developing coronary heart disease in men (RR 0.59; 95% CI 0.48-0.74; p<0.001) and weakly also in woman (RR 0.89; 95% CI 0.79-1; p<0.05) (Figure 23).

In sensitivity analysis, results held true only for men. However, in women if HPS or PROSPER studies were excluded statins were not longer protective against CHD.

No publication bias was found for any of the outcome by applying Begg or Egger test.

Trial	Women/Total n	Age	Lipid entry criterion	Statin	Control	Mean Follow-up	Study design	Year
ACAPS	445/919	62	61,7 LDL 130–159 mg/dL with other risk factors LDL 160–189 mg/dL with none or 1 risk factor	Lovastatin	Placebo	2.8	Double-blinded	1994
AFCAPS/TEXCAPS		67	Total cholesterol, 180–264 mg/dL; LDL 130–190 mg/dL; and HDL <47 mg/dL	Lovastatin	Placebo	5.3	Double-blinded	1998
ALLHAT	5051/10355	NA	LDL, 100–189 mg/dL	Pravastatin	Usual care	4.8	PROBE	2002
ASCOT	1942/10305	NA	Total cholesterol >250 mg/dL	Atorvastatin	Placebo	3	Double-blinded	2003
HPS	1816/5963	NA	Total cholesterol >135 mg/dL	Simvastatin	Placebo	5	Double-blinded	2003
MEGA	5356/7832	60	Total cholesterol levels >220 mg/dL	Pravastatin	Diet	5.3	PROBE	2006
PROSPER	3000/5804	75	Total cholesterol >180 mg/dL	Pravastatin	Placebo	3.2	Double-blinded	2002

Table 5. Trials assessing statins in primary prevention in women (adapted from **Publication 5**). Abbreviations: n: Number. NA: Not Available. PROBE: Prospective randomized open blinded end-point.

Total mortality (men)

Trial		RR (95% CI)	Events Placebo	Statin
ACAPS		0.32 (0.03, 3.03)	3/230	1/242
AFCAPS		0.99 (0.71, 1.37)	70/2803	69/2805
ALLHAT		0.99 (0.86, 1.14)	NR/2630	NR/2645
MEGA		0.79 (0.45, 1.39)	27/1248	21/1228
WOSCOPS		0.78 (0.61, 1.00)	135/3293	106/3302
Overall comparison p= 0.22		0.93 (0.83, 1.04)	NA/10204	NA/10222

Heterogeneity p = 0.408 ; I-squared = 0.0%

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Favours Statins Favours Placebo

Total mortality (women)

Trial		RR (95% CI)	Events Placebo	Statin
ACAPS		0.09 (0.00, 1.70)	5/227	0/218
AFCAPS		1.53 (0.61, 3.81)	7/498	11/499
ALLHAT		0.98 (0.82, 1.17)	NR/2540	NR/2511
MEGA		0.74 (0.45, 1.23)	39/2718	22/2638
Overall comparison p= 0.61		0.96 (0.81, 1.13)	NA/6210	NA/5866

Heterogeneity p = 0.207 ; I-squared = 34.2%

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Favours Statins Favours Placebo

Figure 22. RRs for Total Mortality in men (top) and women (bottom). Solid squares represent ORs in trials and have a size proportional to the number of events. 95% CI for individual trials are denoted by lines and those for the pooled ORs by empty diamonds.

CHD events (men)

Events

Trial	RR (95% CI)	Placebo	Statin
AFCAPS	0.43 (0.34, 0.55)	5/230	0/218
ASCOT LLA	0.41 (0.31, 0.54)	174/2803	109/2805
ALLHAT	0.84 (0.71, 1.00)	NR/2645	NR/2659
HPS	0.82 (0.74, 0.91)	580/2083	471/2064
MEGA	0.45 (0.29, 0.70)	49/1248	31/1228
PROSPER	0.56 (0.48, 0.65)	279/1408	222/1396
WOSCOPS	0.69 (0.57, 0.83)	248/3293	174/3302
Overall comparison p= 0.0001	0.59 (0.48, 0.74)	NA/13710	NA/13672

Heterogeneity p = 0.0001; I-squared = 89.1%

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Favours Statins Favours Placebo

CHD events (women)

Events

Trial

Trial	RR (95% CI)	Placebo	Statin
AFCAPS	0.53 (0.21, 1.34)	5/227	0/218
ASCOT LLA	1.10 (0.57, 2.13)	17/963	19/979
ALLHAT	1.02 (0.81, 1.28)	NR/2540	NR/2511
HPS	0.76 (0.62, 0.94)	168/902	130/914
MEGA	0.74 (0.45, 1.23)	36/2718	26/2638
PROSPER	0.96 (0.77, 1.19)	137/1505	125/1495
Overall comparison p= 0.05	0.89 (0.79, 1.00)	NA/8855	NA/8755

Heterogeneity p = 0.297; I-squared = 17.9%

.2 .5 1 2 5
Favours Statins Favours Placebo

Figure 23. RRs for CHD in men (top) and women (bottom). Solid squares represent ORs in trials and have a size proportional to the number of events. 95% CI for individual trials are denoted by lines and those for the pooled ORs by empty diamonds.

DISCUSSION

Surrogate end points and cardiovascular events

This study shows that the use of surrogate end point such as IMT or LVH progression does predict the risk of cardiovascular events occurence. These results indicate that they cannot substitute the value of well conducted clinical trials for the assessment of cardiovascular prevention treatments.

Carotid IMT regression and cardiovascular events

These results indicate that carotid IMT changes (regression or progression) do not predict the risk of cardiovascular events in subjects with intermediate or high cardiovascular risk (Figure 8).

This observation held true when the relationship was separately assessed for different categories of drugs, in primary or secondary prevention and when potential effect modifiers were introduced in the analytic statistical modeling (see Results).

Although carotid IMT is currently included among organ damage indicators in major cardiovascular guidelines (7), and increased IMT impacts on therapeutic strategy in individual subjects (8), its use as a surrogate end point in clinical trials and interpretation of IMT changes as predictors of clinical benefits remain debated, as also recently reported by the U.S. Preventive Services Task Force (146, 147). This is in contrast with other organ damage indicators such as microalbuminuria where favorable cardiac and renal outcomes have been demonstrated (148).

However, the findings of this study do not affect the role of a baseline measurement of carotid IMT as a risk marker (6, 149). In particular,

high IMT values have been shown to be a proxy of atherosclerosis elsewhere in the circulation (150).

Hypothetic mechanisms behind these results are multiple. One hypothesis might be related to complexity of the IMT thickening that is not only determined by atherosclerotic risk factors (151). In fact, the role of IMT as a marker of atherosclerosis has been challenged (152, 153). Thus, it is conceivable that the multifactorial determinants of IMT may reduce the clinical strength and statistical significance of IMT progression as predictor of cardiovascular outcomes when interventions are targeted only on single risk factors (i.e. statins or anti-hypertensives).

The second additional and relevant hypothesis that can explain these findings concerns the assumption that carotid wall injuries are representative of the status of the whole arterial bed in the body, including the coronary tree. Indeed, this has not been proven in the majority of subjects, by pathological post-mortem studies (154, 155) and by clinical studies (156), clearly indicating that in the majority of patients, carotid lesions, including atherosclerotic plaques, are dissociated from coronary lesions.

Finally, since atherosclerotic plaques grow longitudinally along the carotid axis, faster than they thicken, IMT might be a less sensitive measure of plaque evolution (157). In fact, it was demonstrated that carotid plaques are a more sensitive and representative measure of the atherosclerotic burden than IMT, with higher predictive value for cardiovascular events (158, 159). In addition, the fact that IMT association with coronary heart disease was influenced by change in systolic blood pressure (see sensitivity analysis results), might strengthen the hypothesis that IMT is influenced by mechanisms such as the shear stress and wall reactivity rather than pure atherosclerotic

processes.

LVH regression and cardiovascular events

In detail, for LVH this is the first study reporting a meta-regression investigating the correlation between quantitative changes in LVH and risk of clinical events. The results of this analysis, that gathered a number of patients and events higher than any previous meta-analysis on LVH, could not demonstrate a continuous association between LVH and risk of adverse major clinical events.

These results contradict the previous evidence where LVH was assessed qualitatively (presence vs absence) and not continuously (i.e. comparing patients with complete regression of LVH to patients with persistence or development of new LVH) (51, 52).

These findings are not consistent with the association found by Schillaci and colleagues of progressively greater LVH values and cardiovascular events in hypertensive patients (53). In that study, a significant continuous relationship between quintiles of echocardiographically measured LVH and cardiovascular outcomes was observed, indicating an adverse effect on prognosis even for LVH values in the upper normal limits. Thus, it was conceivable that even partial reversal of LVH could have been associated with prognostic benefit. This hypothesis could not be demonstrated with this analysis. However, this finding does not impact the favorable prognostic value of LVH regression, demonstrated in previous qualitative analyses (51,52), that remains a strategic target of antihypertensive treatments. However, these results discourage the use of quantitative serial measurements of LVH as a surrogate end point.

Cardiovascular prevention. Filling the gaps in Evidence Based Medicine

The efficacy of CCBs in cardiovascular prevention

In contrast with previous studies (80, 92), this meta-analysis shows that dihydropyridine CCBs reduce the risk of all cause death (Figure 11), not only against placebo but also against other drugs. This result was independent from blood pressure reduction. Despite not significant, there was a trend for cardiovascular death reduction with CCBs (Figure 12). It must be said that out of the 24 trials, only 17 disclosed results about cardiovascular death. Therefore, it could be possible that with further data available, also a benefit against cardiovascular death would have become overt.

This study also showed a benefit of CCBs against placebo in preventing heart failure (Figure 14), which has never been shown previously (80, 92). This result was influenced by the blood pressure reduction, as shown by the meta-regression analysis (Figure 17). However, when CCBs were compared to diuretics/betablockers were not protective as compared to placebo for this outcome. It must also be stated that the most frequent adverse event associated with dihydropyridine CCBs is ankle edema, which sometimes could have been misinterpreted as congestive heart failure. In fact, some CCBs trials may be biased by the discontinuation of baseline antihypertensive therapy in patients previously receiving a diuretic that could have unmasked heart failure.

Although specific pathophysiological effects of single drug class may exert a protective effect on heart failure, blood pressure lowering is likely the most relevant protective mechanism to prevent this outcome.

As regarding to the risk of MI, CCBs provided similar benefit as compared to other drugs. The historical concern assigned to the short

acting CCBs for MI has not been transferred to long acting ones, as also already shown by previous meta-analyses (82, 90).

In our study it has been confirmed that dihydropyridine CCBs reduced the risk of stroke and this was true also when they were compared to ACE-Is. The mechanism behind that is not entirely clear and it whether these findings have implications for the long-term prevention of strokes remains to be proven.

The role of ARBs compared to ACE-Is in patients without LVSD

These results show that ARBs are not as effective as ACE-Is in reducing the risk of cardiovascular events in patients without LVSD. Whilst ACE-Is reduced the risk of all major cardiovascular events (but not cardiovascular death), new onset heart failure and diabetes mellitus, ARBs were only effective in reducing stroke and new onset of diabetes mellitus.

These findings confirm and extend a previous meta-analysis regarding ACE-Is (94), adding several more trials (corresponding to 23,986 additional patients) (161-167). This study may fill a gap into the current evidence based medicine, since no previous meta-analysis has ever investigated the effects of ARBs compared with placebo or standard therapy in patients without LVSD. In fact, the evidence so far has only been available for patients with heart failure (168, 169).

In another study (170) of randomized clinical trials of renin-angiotensin aldosterone system inhibitors, a benefit of these classes of drugs (ACE-Is – ARBs – Spironolactone) towards cardiovascular events was shown, however with no separated analysis for each class of drugs.

No separate analysis for ACE-Is and ARBs was provided by a more recent meta-analysis by McAlister and colleagues (171) that examined trials including normotensive patients with atherosclerosis. Furthermore, patients with heart failure were also included.

ARBs may represent an alternative to ACE inhibitors, mainly in cases where an ACE inhibitor is not tolerated (172, 173). As a result of the more selective renin angiotensin system inhibition provided by ARBs and therefore of their better tolerability, the large-scale use of this group in heart failure seems to be reasonable despite the related evidence still being contradictory and not convincing (174).

Biological explanations behind these results may only be speculated. Whilst ACE-Is inhibit the conversion of Angiotensin I to Angiotensin II, ARBs selectively inhibit the binding of Angiotensin II to AT1 receptors. The presumed pharmacological benefit of ACE-Is over ARBs might be related to the degradation of bradykinin, hence enhancing protective cardiovascular mechanisms (174). In fact, bradykinin inhibits platelet aggregation, reduces the level of plasminogen activator inhibitor-1, and also exerts vasodilatory effects by elevating prostacyclin and nitric oxide (NO) levels (175, 176). Furthermore, bradykinin significantly inhibits endothelial apoptosis, thus contributing to endure endothelial normal functioning. Consequently, higher bradykinin levels are very likely to reduce the progression of atherosclerosis (177). In similar studies conducted with ARBs, no similar beneficial effects on endothelial apoptosis could be found (178).

In addition, recent studies have shed more light on the role of AT1 and AT2 receptors. Previously, it was thought that selective AT1-receptor inhibition by ARBs would have enhanced some presumed beneficial effects of AT2 receptors (i.e. cell regeneration, vasodilation etc.) (179). Instead, new studies have shown that under certain circumstances, AT2-receptor activity can even be harmful with pro-atherogenic and pro-inflammatory effects, and hence contributing to the rupture of atherosclerotic plaques, leading to acute coronary events (180).

The efficacy of statin therapy for primary cardiovascular prevention in women and men

This study showed that statin therapy reduced the risk of CHD events in men without prior cardiovascular disease. This substantial protective effect remained unchanged even when trials only partially of primary preventions were excluded (133, 134). Also excluding ALLHAT trial (83) from the analysis, that was the only trial not reporting a significant risk reduction, a significant benefit towards CHD events remained.

However, for women treated with statins for primary prevention, CHD risk reduction was only of borderline significance. Furthermore, excluding HPS trial (133), the borderline significance disappeared, becoming clearly not significant. Indeed, since it is already well known that statins are effective for CHD in secondary prevention (114), the great proportion of patients with prior cardiovascular disease included in HPS study has probably influenced the results of this study.

Statin therapy did not reduced total mortality for both men and women without previous cardiovascular disease over the 3.9 years average study duration. However, longer follow up may be necessary to show reduced mortality.

Previous literature had already shown that statins reduce cardiovascular events but not mortality in primary prevention. However, the results were not stratified by gender and about 70% of the participants included in that study were men (115).

Another meta-analysis specifically tailored in assessing cardiovascular events in women found a reduction in cardiovascular events, however they did not perform a separate analysis for primary and secondary prevention (181).

The mechanisms explaining these results are unclear. It is known that women have a lower risk of cardiovascular disease than men at a

given age, possibly because of the oestrogen related benefit towards cardiovascular events (182). However, they do still ultimately develop disease, making vascular disease the leading cause of death in women (183)

It has been shown that statins are associated to an increased risk of diabetes mellitus, with a higher risk for women (184). Sex-dependent higher risk of incidental diabetes mellitus in women may be also explained by the relationship among oestrogens, testosterone and insulin resistance (185).

CHAPTER V

Limitations

This study has got some limitations, either related to the meta-
analysis methodology or to the nature of the topics investigated.
The results of these meta-analyses derive from aggregate and not
from individual patients data. This may have impacted on the
definitions of cardiovascular events since their validation could differ
across the trials.

Given the unavailability of access to individual study participant data,
complete covariates data were not available from all trials and this
may have affected the potential effect modifiers analysis. However, it
has been reported that, when the number of studies and of subjects
in studies is not small, meta-regression with aggregated data is
reliable and meaningful
(121).

Furthermore, some clinical outcomes were not available from the
published papers of the trials included in these meta-analyses,
however, despite contacting the study investigators for supplemental
data, response rate was low.

For each topic investigated there are limitations to consider.
For the carotid IMT meta-regression analysis, technical aspects
concerning the reproducibility of serial within-individual changes and
lack of standardization of IMT measurements may play a role to
explain the findings of the present study in which trials using different
methodological approaches were pooled. Indeed, carotid IMT
measurements are prone to generate variability in follow-up studies,
mostly sonographer dependent. However, in controlled clinical trials,
measurement variability has been decreasing, owing to technical
improvements, standardization, and training (186). To take into
account this potential limitation, a sensitivity analysis with the year of

trial publication as covariate was performed. This did not show a significant impact on the results. Furthermore, in multicenter trials, images are handled and IMT measurements recorded off line in a core ultrasound laboratory that limits, likely substantially, technical errors in measurements. In fact, considering the potential suboptimal standardization of IMT measurement in small studies, a sensitivity analysis excluding studies that did not measure IMT in a central core laboratory was performed, and the results again did not significantly change.

For the LVH meta-regression analysis, the incorporation of studies using either echocardiographic or electrocardiographic assessment of LVH could be perceived as a limitation. However, both ways of measurement are well validated and established in the clinical practice. The studies included in the analysis were different in terms of length of follow-up, which was quite short in some of them. This raises the possibility that longer follow- up intervals could potentially influence the results.

For the ACE-Is and ARBs meta-analysis, it must be considered that the characteristics of the populations were different. ACE-Is trials were mostly conducted in patients with coronary or other vascular atherosclerotic disease, whilst ARBs trials were mostly conducted in patients with diabetes mellitus or impaired glucose intolerance. Furthermore, this study does not represent a direct comparison between ACE-Is and ARBs, which could only be adequately assessed with ad hoc trials. Only one large trial directly compared an ACE-I versus an ARB, the ONTARGET trial. However, no significant difference between telmisartan and ramipril on major CV outcomes was found, although no placebo arm was available (187).

Finally, regarding statins in primary prevention, data on adverse outcomes were not available, therefore it was not possible to check whether these could have affected the results.

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